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X-RAY DIAGNOSIS OF ILEUS

THE VALUE OF ROENTGENOGRAMS IN SIMPLE AND STRANGULATED OBSTRUCTION
AN EXPERIMENTAL STUDY[1]

ALTON OCHSNER, M.D., F.A.C.S., NEW ORLEANS, LOUISIANA

IN acute intestinal obstruction, as in the majority of surgical emergencies, early diagnosis is of utmost importance. All else being equal, the earlier the relief of an intestinal occlusion, the better is the prognosis. Van Beuren has aptly stated, "The longer a patient with intestinal obstruction lives before operation, the sooner he dies afterward." Any procedure, therefore, facilitating the early diagnosis of this condition which yearly claims so many lives should, indeed, be more extensively used.

The roentgen diagnosis of ileus has been used much more extensively in the past 5 years than previously although its true value as a diagnostic procedure in ileus, I am sure, is not sufficiently appreciated. Obviously, the administration of a contrast substance by mouth in suspected ileus is contra-indicated, and in such instances, only plain roentgenograms of the abdomen should be obtained. The procedure first advocated by Schwarz in 1911 has been used extensively, as evidenced by the numerous reports (Assmann, Case, Weil, Kloiber, Milhaud, Kolbfleisch, Meyer and Brams, Davis, Rabwin, Trémolières, Zadoc-Kahn, Kwong, Weber, Milligan and Simon). The value of plain roentgenograms of the abdomen consists of visualization of accumulated gas or gas and fluid proximal to the point of obstruction. Normally gas is present only in the stomach and in the large bowel and when found in the remaining portions of the intestine indicates the presence of either a mechanical or adynamic ileus. The relative values of roentgenograms obtained in such a way that the junction between gas above and fluid below might be visualized and those obtained to demonstrate an accumulation of gas alone have been discussed by many authorities. In order to visualize fluid levels, i.e., the junction between the fluid below and the gas above, it is necessary to obtain the roentgenogram by placing the patient, the X-ray plate, and the tube in such positions that the rays will parallel the surfaces of the fluid contained within the intestine. This is accomplished by anteroposterior roentgenograms with the patient in the upright position or with the patient lying on one side or lateral roentgenograms with the patient in the supine position. Gas accumulation alone can be demonstrated on anteroposterior roentgenograms taken with the patient in the supine position. The advantage of the former is that the contrast between the gas and fluid gives a very definite picture. The advantage of the latter is that the usual technique of obtaining roentgenograms need not be varied. Assman, Case, Weil, Davis, Meyer and Brams, Rabwin and Carter, Trémolières, Zadoc-Kahn and Kwong, Weber, Milligan and Simon are

[1] From the Department of Surgery, Tulane University School of Medicine, New Orleans.

TABLE I.—JEJUNUM

Time in hours	Simple obstruction of jejunum					Strangulated obstruction of jejunum				
	Horizontal		Upright			Horizontal		Upright		
	Gas	Colon	Gas	Fluid	Colon	Gas	Colon	Gas	Fluid	Col
1						37	25	37	0	2
3	25		25	25		55	44	50	25	4
4	31	37	31	12	25					
5	50	50	50	25	37	56	56	56	31	5
7	62	41	62	46	37	75	64	75	56	6
9	75	50	75	58	25	75	62	75	62	6
11	83	50	75	66	37					
26	66	50	83	75	75					

of the opinion that visualization of the gas is sufficient and that the demonstration of fluid levels is unnecessary. On the other hand, Schwarz, Hoesslin, Weil, Bensaude and Gunéaux, Kloiber, Milhaud, Wynen, Kolbfleisch, Martens, Ochsner and Granger consider the demonstration of fluid levels in cases of ileus of sufficient importance to have roentgenograms made in such a way that they may be visualized.

Relatively little work has been done to determine the time at which X-ray evidence of ileus becomes positive. Kloiber believes that the accumulation of gas in the intestine can be demonstrated roentgenographically within 5½ hours after the beginning of obstruction. Case states that within 6 to 8 hours enough fluid and gas accumulate within the bowel proximal to the obstruction to be visualized by the roentgen rays. Wangensteen and Lynch found in animals that within 4 to 5 hours after complete occlusion gaseous distention proximal to the obstruction could be demonstrated roentgenographically. They believed that the accumulation of fluid proximal to the obstruction was less marked than that seen in humans unless the animal was given a saline infusion. They also found that there was less distention associated with strangulated than with simple obstructions. Subsequently, Goehl, Lynch, Borman, and Wangensteen, working with varying degrees of strangulation in isolated intestinal loops found that the gas accumulation as demonstrated roentgenologically did not occur as early as in simple obstruction. This latter finding would seem to vitiate the value of roentgenograms as an early diagnostic procedure in ileus, because it is in strangulated obstruction that early operative interference is especially indicated. It is a well known fact that the prognosis is much worse and the urgency for operative relief is much greater in the presence of strangulation than in simple obstruction. The value of plain roentgenograms of the abdomen in the early diagnosis of ileus, however, is exemplified by the results reported by Rabwin and Carter. The mortality rate during the 8 months that roentgenological diagnoses of ileus were made was 23 per cent as compared with 53 per cent, 37 per cent, and 40 per cent, respectively, for similar periods of time in 3 previous years.

In order to determine the relative values of roentgenograms taken in such a way that fluid levels might be demonstrated and those taken to visualize the presence of gas alone and in order to compare the roentgenographic findings in simple and strangulated ileus, the present investigation was undertaken. Twenty-three dogs were used in the experiment. In 7, obstructions were produced in the jejunum, of which 3 were simple obstructions and 4 were strangulated obstructions. The simple obstructions were accomplished by tightly[1] tying heavy binding tape around the gut. Strangulated obstructions were produced in a similar manner but in addition, the blood supply to the bowel proximal to the obstruction was interfered with by tying rubber bands around the individual vessels in the

[1]The tape was not tied tight enough to produce necrosis.

mesentery, which ultimately resulted in gangrene. In 14 animals, obstructions of the ileum were produced, 9 of the simple and 5 of the strangulated varieties. In 2 animals, a strangulated obstruction of the sigmoid was made. Plain roentgenograms of the abdomen were made at varying periods of time after the production of the obstruction, one with the animal in the upright position, and one with the animal in the horizontal position. The obtaining of roentgenograms with the animals in the upright and horizontal positions was facilitated by the use of an especially constructed animal board previously described by Ochsner and Gage. In all, 109 observations were made, making a total of 218 roentgenograms, 109 obtained in the upright and 109 in the horizontal positions. In the reading of the plates, the degree of gas or fluid accumulation was expressed as varying from + to + + + +, + representing approximately 25 per cent and + + + + representing gaseous distention of the intestine of the entire abdomen. Subsequently these were transferred into percentages and are used as a basis for the calculations that appear on the tables.[1]

In simple obstructions of the jejunum (Table I), there were no X-ray evidences of accumulation of gas or gas and fluid earlier than 3 hours after the production of the obstruction. However, roentgenograms taken 3 hours after the production of the obstruction were positive for gas accumulation (Fig. 1), which increased in amount as the time interval increased. The accumulation of gas apparently occurred more rapidly than did the accumulation of fluid (Table I). As early as 4 hours after the obstruction, there was evidence of accumulation of gas in the colon, i.e., distal to the point of obstruction, the amount of which fluctuated considerably, indicating that at times, the gas would be evacuated. In general, however, it increased as the time interval increased.

In strangulated obstructions of the jejunum (Fig. 11), as early as 1 hour after the production of the strangulated obstruction, there were accumulations of gas, both in the bowel proximal to the obstruction and also in the colon, distal to the obstruction. There were no evidences of accumulations of fluid. The accumulations of gas increased rapidly in amount, much more rapidly than in the simple obstructions. As early as 3 hours after the production of the obstruction, there were evidences of fluid formation, as could be demonstrated by fluid levels in the roentgenograms taken in the upright position. The gaseous distention of the colon distal to the obstruction also increased, but less so than that in the bowel proximal to the obstruction (Fig. 2). From these results, it is evident that in strangulated obstruction of the jejunum, X-ray evidence of the obstruction is positive as early as 1 hour after the production of the obstruction, whereas evidence of simple obstruction does not become positive until 3 hours after the obstruction. There also occurred distal to the obstruction, principally in the colon, gaseous dilatation, which is probably reflex in origin. This was positive in the strangulated obstructions as early as 1 hour after the obstruction whereas in the simple obstructions, it did not occur until 4 hours after the obstruction. The roentgenographic signs not only occurred earlier but were more marked in the strangulated obstructions than in simple obstructions of the jejunum (Fig. 3).

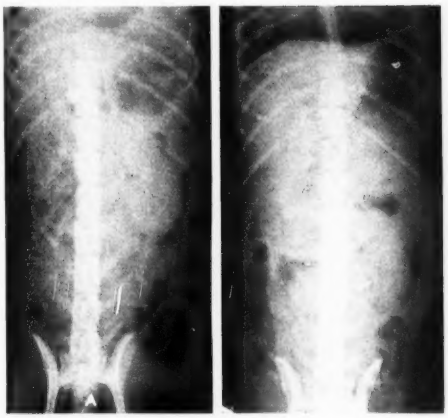

Fig. 1. Roentgenograms taken 4 hours after simple obstruction of the jejunum. A, Horizontal position; B, upright position. There is an accumulation of gas as shown in both roentgenograms but no evidence of fluid levels.

[1] The percentages so obtained are obviously not absolute but only relative and are of value only when used in a comparative study.

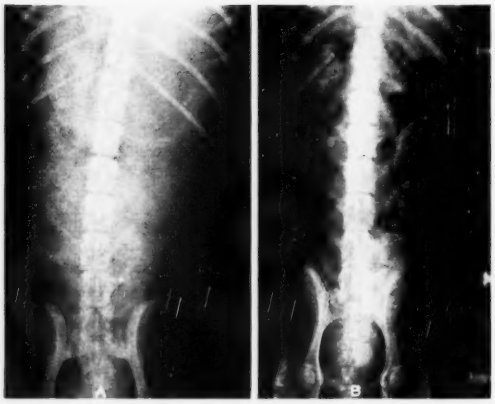

Fig. 2. Roentgenograms of 3 hour obstructions of the jejunum. There is considerably more gas in the strangulated obstructed gut, B, than in that with simple obstruction, A. In strangulated obstruction, B, there is also considerable accumulation of gas in the colon; i.e., distal to the point of obstruction. Both roentgenograms were made with the animals in the horizontal positions.

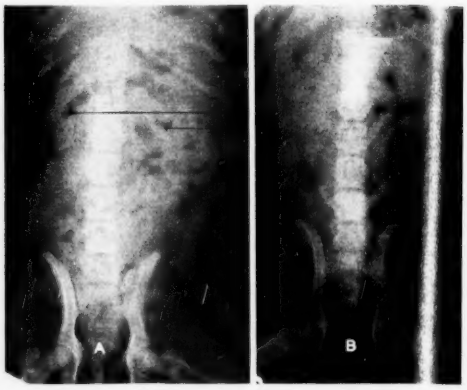

Fig. 4. Roentgenograms of strangulated obstruction of the jejunum taken 1 hour after the production of obstruction. The roentgenogram taken with the animal in the upright position, A, shows gas accumulation and several fluid levels, as indicated by the arrows, whereas the roentgenogram of the animal taken in the horizontal position, B, shows accumulation of gas above.

In simple obstructions of the ileum (Table II), as early as 1 hour after the obstruction, there were X-ray evidences of accumulation of gas, both proximal to the point of obstruction and in the colon, distal to the obstruction. The earliest evidences of fluid accumulation in simple obstructions were found 3 hours after the obstruction. The accumulation of both gas and fluid rapidly increased as the time interval increased. The amount of gas accumulation in the colon fluctuated considerably, probably due to the fact that the gas distal to the obstruction was evacuated from time to time. In general, however, it also increased as the time interval increased. In strangulated obstructions of the ileum, there occurred as early as 1 hour after the production of the obstruction, an accumulation of both gas and fluid proximal to the obstruction (Fig. 4). There were no evidences of gas in the colon. The gas and fluid accumulation rapidly increased as the time interval increased. It is evident that in the present investigation X-ray evidence of ileus (accumulation of gas and fluid) was more marked in strangulated obstructions than in simple obstructions of the ileum (Figs. 5 and 6). There were also greater accumulations of gas and fluid in obstructions of the ileum than in similar obstructions of the jejunum (Figs. 7 and 11).

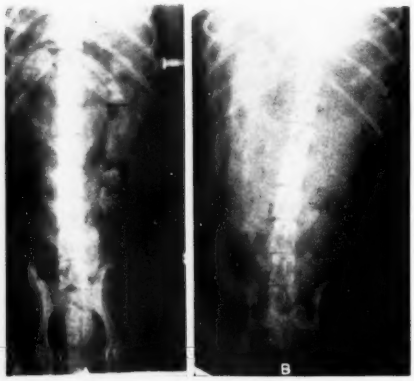

Fig. 3. Roentgenograms of 7 hour obstructions of the jejunum. There is considerably more gas accumulation in A (strangulated obstruction) than in B (simple obstruction). Both roentgenograms were made with the animals in the horizontal positions.

In only 2 animals were X-ray observations made of strangulated obstructions of the sigmoid. In both as early as 1 hour after the production of the strangulated obstruction, there was considerable accumulation of gas and fluid (more of the former than the latter) proximal to the obstruction (Fig. 8 This

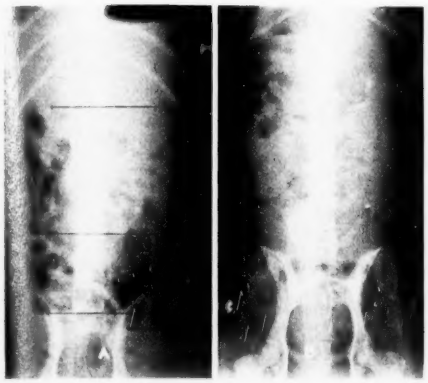

Fig. 5. Roentgenograms of 5 hour obstructions of the ileum, both roentgenograms being taken in the upright position. A, Strangulated obstruction of the ileum; B, simple obstruction of the ileum. There is a much greater accumulation of gas and fluid in the strangulated obstructed gut, A, than in the simple obstructed gut, B. In the roentgenogram of the animal with strangulated obstruction of the ileum, A, there is considerable gas accumulation in the colon that is distal to the point of obstruction.

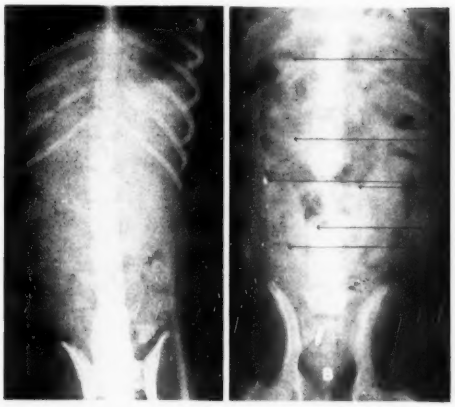

Fig. 6. Roentgenograms of 7 hour obstructions of the ileum. A, Simple obstruction; B, strangulated obstruction. There is a much greater accumulation of both fluid and gas in the strangulated obstruction, B, than in the simple obstruction, A.

rapidly increased as the time interval increased (Fig. 9). In comparing the abdominal roentgenograms of animals with obstructions of the jejunum, ileum, and sigmoid, it is evident that the lower the obstruction, the more marked are the roentgenographic findings (Figs. 7 and 10).

TABLE II.—ILEUM

Time in hours	Simple obstruction of ileum					Strangulated obstruction of ileum				
	Gas	Colon	Gas	Fluid	Colon	Gas	Colon	Gas	Fluid	Colon
1	12	0	25	0	12	25	0	25	25	0
3	37	0	50	25	12	58	41	66	58	33
4	62	12	62	25	12	66	50	66	66	50
5	66	41	66	25	41	90	40	90	70	45
7	66	39	66	36	36	95	55	95	80	60
9	66	33	66	66	33	100	50	100	100	50
11	75	40	70	55	45					
24	90	50	90	60	60	87	62	87	81	62
30	95	60	95	80	65					
48	95	55	90	90	55					
55	100	75	100	91	75					
75	100	62	100	100	62					
						Strangulated obstruction of sigmoid				
						Gas	Colon	Gas	Fluid	Colon
1						62	62	62	37	62
4						100	75	100	75	75
6						100	100	100	75	100
10						100	100	100	100	100

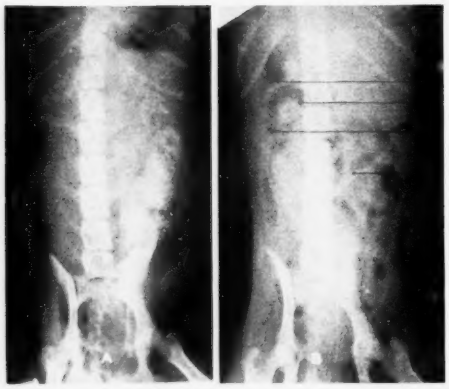

Fig. 7. Roentgenograms of 3 hour strangulated obstructions of the jejunum, A, and ileum, B. There is a much greater accumulation of both gas and fluid (indicated by arrows) in the obstruction of the ileum, B, than in the obstruction of the jejunum, A. Both roentgenograms were taken with the animal in the upright position.

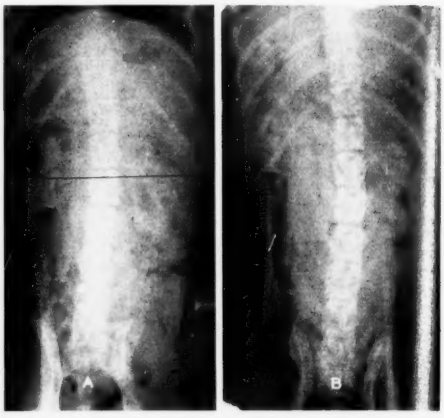

Fig. 8. Roentgenograms of strangulated 2 hour obstructions of the sigmoid. There is an accumulation of gas in both roentgenograms. Fluid levels are visualized in the roentgenograms taken in the upright position, A. The roentgenogram taken in the horizontal position, B, shows the presence of gas even though the plate was taken only 1 hour after obstruction.

DEDUCTIONS FROM EXPERIMENTS

The value of roentgenography in the early diagnosis of ileus is exemplified by the present investigations. Simple obstructions of the ileum could be demonstrated roentgenologically as early as 1 hour after the onset of the obstruction by the accumulation of gas proximal to the obstruction. It is true that the amount of gas present in such simple obstructions within the first hour was relatively slight, but it was of sufficient quantity to be distinctly abnormal, demonstrating that roentgenography as early as 1 hour after the obstruction could be of value clinically as a diagnostic procedure. More important, however, is the fact that in strangulated obstructions of the jejunum, ileum, and sigmoid, there were marked X-ray evidences of the obstruction as early as 1 hour after the obstruction, the accumulation of gas being more marked than that which was seen in the simple obstructions. In the obstructions of the jejunum and ileum, as early as 1 hour after the obstruction, there were also accumulations of fluid which were not present in simple obstructions of the jejunum. The fact that roentgenograms of the abdomen taken 1 hour after strangulated obstructions are positive is especially significant because as mentioned, operative relief of strangulated obstruction must be secured earlier and is more imperative than that of simple obstruction. A simple obstruction of the bowel in which there is no interference with the blood supply, especially if the lower portion of the intestine is involved, offers a relatively good prognosis. The urgency for operation is, however, materially increased as soon as there is an interference with the blood supply to the gut. These results do not coincide with those of Goehl, Lynch, Borman, and Wangensteen, who found less distention associated with strangulated obstructions than with simple obstructions. The discrepancy in the results may be due to the fact that Goehl *et al.* worked with isolated intestinal loops whereas in the present investigation, the obstruction was produced by occluding the intestine and at the same time interfering with the blood supply in the mesentery, a factor which I feel is more apt to be encountered clinically, except in cases of volvulus and certain cases of hernia. The greater accumulation of gas and fluid in strangulated than in simple obstruction appears paradoxical, but the explanation may be as follows: As a result of the interference with the blood and also the nerve supply to the gut, a local paresis and decreased ab-

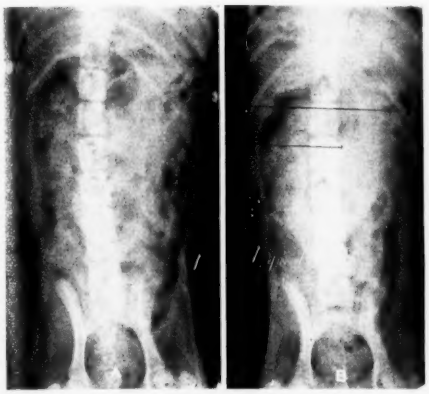

Fig. 9. Roentgenograms of 4 hour strangulated obstructions of the sigmoid. There is considerable accumulation of gas in both plates, that taken in the upright position, B, and that in the horizontal position, A. Fluid levels are visualized in the plate taken in the upright position, B.

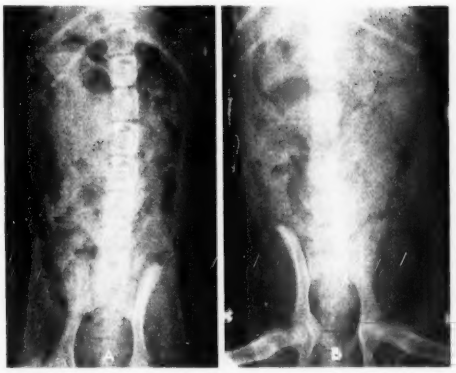

Fig. 10. Roentgenograms comparing 4 hour strangulated obstructions of the sigmoid and ileum. In the strangulated obstruction of the sigmoid, A, there is a great deal more accumulation of gas than in the strangulated obstruction of the ileum, B. Both roentgenograms were taken in the horizontal positions.

sorbability of the bowel probably occurs. Gas and fluid from the normal intestine above the area of strangulation are forced by peristalsis into the dilated paretic portion of bowel where they remain because of obstruction and diminished absorbability of the intestine. This would explain the discrepancy between our results and those of Goehl *et al.*, who were unable to obtain early evidences of gaseous distention of strangulated isolated loops of intestine. Ultimately gaseous distention of strangulated intestine will occur as the result of normal bacterial proliferation and gas production, which however occurs too late to be of any diagnostic value.

It was found in the present investigation that the lower the obstruction, the greater was the accumulation of gas and fluid (Figs. 7 and 10). This may be due to the fact that as a rule in the lower obstructions, the blood supply of a greater length of intestine was interfered with than in the higher obstructions. Also in the lower obstructions more gas, which can be forced into the dilated, paretic portion of strangulated bowel, may form proximal to the obstruction. It may seem that roentgenography is of relatively less value in obstructions high in the intestinal tract than in low obstructions because the X-ray evidences of low obstructions are more marked than those of high obstructions. However, in the present investigation, it was shown that as early as 1 hour after the production of the high strangulated obstructions there was sufficient accumulation of gas to make a positive diagnosis of ileus. Moreover, as early as 3 hours after the production of the obstruction, there was in addition, considerable accumulation of fluid.

The relative values of obtaining roentgenograms of the abdomen in the routine anteroposterior position with the patient in the supine position or obtaining them in such a way that the fluid levels could be visualized has been disputed. The author has always felt that roentgenograms demonstrating fluid levels are more valuable than those in which only accumulations of gas can be shown. In the present investigation, however, it is demonstrated than the accumulation of gas occurs earlier and is more marked than is the accumulation of fluid. It is also evident that the earliest roentgenographic findings in ileus both of the simple and strangulated varieties is gaseous dilatation of the bowel proximal to the obstruction, which can be demonstrated in the roentgenogram taken in the ordinary manner. In those obstructions which had existed longer than 3 hours, however, there was sufficient accumulation of fluid so that

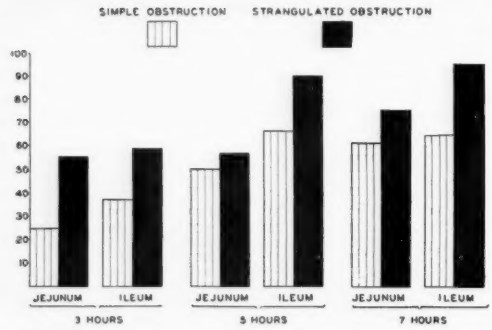

Fig. 11. Graphic representation illustrating the relative amounts of gas accumulation in the bowel in simple and strangulated obstructions of the jejunum and the ileum, as demonstrated roentgenologically at varying periods after the production of the obstruction.

multiple fluid levels could be demonstrated. Even though gas accumulated earlier and more rapidly than fluid in both simple and strangulated intestinal obstructions, the author still believes that because, when fluid levels can be demonstrated, they produce such a typical pathognomonic picture, roentgenograms when possible, should be made in such a way that fluid levels may be visualized. Such roentgenograms can be obtained with relatively little difficulty, even in the extremely ill patient, either by obtaining a lateral roentgenogram with the patient in the supine position or an anteroposterior roentgenogram with the patient lying on the side. In the majority of instances, patients are not too ill to assume the sitting position so that an anteroposterior roentgenogram can be obtained. In this way, roentgenograms can demonstrate the junction between the fluid below and the gas above, which is of diagnostic importance. Even though the obstruction is of such short duration that an accumulation of fluid has not occurred, gaseous distention can be visualized on roentgenograms taken in this way as readily as in roentgenograms taken in the ordinary position.

Significant is the finding that in the majority of observations in the present investigation and in all of those in which the obstruction had existed 4 or more hours, there was an accumulation of gas in the colon distal to the obstruction. This is undoubtedly due to a reflex dilatation of the colon. It occurred much more frequently in the strangulated obstructions than in the simple obstruction. The degree of gaseous distentions varied considerably and did not progressively increase with the time interval as did the amount of gas proximal to the obstruction. This was probably due to the fact that from time to time, passage of flatus may have occurred from the colon distal to the obstruction. Goehl, Lynch, Borman, and Wangensteen observed dilatation of the intestine distal to a strangulated loop of gut and compared it to the paralytic ileus which accompanies peritonitis.

SUMMARY

1. Plain roentgenograms of the abdomen in cases of ileus are extremely valuable as an early diagnostic procedure.

2. The earliest roentgenographic evidence of obstruction consists of an accumulation of gas proximal to the point of obstruction. Gas accumulation occurred earlier and was more marked than was fluid accumulation.

3. In simple obstructions of the jejunum as early as 3 hours and in strangulated obstructions of the jejunum as early as 1 hour after the onset of obstruction, there was sufficient gas accumulation to diagnose ileus roentgenologically.

4. In both simple and strangulated obstructions of the ileum, there was sufficient accumulation of gas as early as 1 hour after the production of the obstruction to make possible a positive X-ray diagnosis. However, the accumulation of gas and fluid was more marked in strangulated than in simple obstructions.

5. The accumulations of gas and fluid were apparently greater the lower the site of obstruction, and were more marked in strangulated than in simple obstructions.

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THE APPLICATION OF SURGERY TO THE HYPOGLYCÆMIC STATE DUE TO ISLET TUMORS OF THE PANCREAS AND TO OTHER CONDITIONS[1]

EVARTS A. GRAHAM, M.D., F.A.C.S., AND NATHAN A. WOMACK, M.D., ST. LOUIS, MISSOURI
From the Department of Surgery, Washington University School of Medicine and Barnes Hospital, St. Louis

THE subject which I have selected to discuss in this the fourth annual Arthur Dean Bevan lecture seemed to me a particularly appropriate one because much of the pioneer work which has attracted attention to the possibility of the surgical relief of this condition has been done by those who have in some way been identified with this city (Chicago). I refer especially to the careful and painstaking work of Rollin Woodyatt on sugar metabolism, to the important cytological investigations of Bensley, and finally to the careful study by Russell Wilder of a case of carcinoma of the islands of Langerhans which was associated with evidence of hypoglycæmia. My particular reason, however, for selecting this subject was the fact that in the last few years at the Barnes Hospital we have had the unusual experience of encountering 6 cases of proved tumor of the islet tissue. In 3 of these the patients were operated upon with successful results, and in the 3 others in which no operation was performed the tumors were found at autopsy. In addition the material obtained at an autopsy at another hospital has been studied by our department of pathology.

Before the discussion of the subject in detail it may be well briefly to review our current conceptions of the regulation of the sugar in the blood. The sugar equilibrium is maintained by the counterplay, under nervous control, of a number of factors of which the secretions of several glands are perhaps the most important. Insulin from the islands of Langerhans of the pancreas tends to diminish the amount of blood sugar; and, on the other hand, the secretions from the medulla of the adrenal gland, from the anterior lobe of the pituitary[2], and from the thyroid all tend to increase it. Despite the antagonistic action of several forces the amount of the blood sugar in normal fasting individuals, that is before breakfast, does not vary greatly but is usually found to be about 0.10 per cent, or about 100 milligrams of sugar in 100 cubic centimeters of blood.

The introduction of insulin as a therapeutic agent was soon followed by dramatic demonstrations of the danger which may arise from reducing the amount of the blood sugar too far below the normal level. Accordingly a syndrome of hypoglycæmia has become recognized. The clinical manifestations of this condition are numerous. It is necessary to mention some of these in order to understand the picture presented by an active tumor of the islands of Langerhans.

The most commonly observed symptoms of hypoglycæmia are a feeling of malaise, lassitude, inability to perform mental or physical work, often accompanied by trembling and sweating. The face may be alternately pale and flushed. There may be a fall in temperature. Simultaneously with these symptoms there is usually a sensation of hunger which may be extreme and even agonizing. Carlson and his associates have shown that hypoglycæmia is associated with violent contractions of the stomach. One of Harris' patients states that he felt as if he would die if he could not have food immediately. Yawning and mental confusion often accompany the sensation of severe hunger. The pulse is usually accelerated. But some of the most important and striking symptoms are related to the nervous system. Mental confusion, resembling alcohol intoxication, is very common, and crises resembling epileptic convulsions have been noted so often that the first diagnosis made in several of the reported cases of island tumors has been that of epilepsy. In most cases, however, it can be

[2] Ordinary commercial pituitary extract which is made mostly from the posterior lobe also increases the blood sugar. The action of adrenalin is supposed to be due to the liberation of sugar from glycogen stored in the liver.

[1] This paper was given by the senior author as the fourth annual Arthur Dean Bevan Lecture before the Chicago Surgical Society and the Chicago Institute of Medicine on December 16, 1932.

noted that the crises are different from those of true epilepsy of the grand mal type. Sigwald in a recent excellent monograph on hypoglycæmia states, "Most often these attacks are partial, limited, intermittent, and irregular; the contractures have abnormal characteristics; one can observe hysteriform crises with contracture in the arc of a circle and great agitation, or tetaniform crises with permanent contracture in opisthotonus or in another attitude. These extensive convulsions deserve the name of 'epileptiform crises'." Convulsions limited to one side of the body and even to the face or to the extremities have been recorded. Amnesia is another common symptom of great value. The patients seldom remember what they have done or said during the periods of mental and psychic abnormality. In some cases even localizing signs of disorder of the central nervous system, such as a Babinski sign, disturbances of the pupils, etc., have been noted in connection with the hypoglycæmic state. In the more severe cases, coma is frequently observed. It is unnecessary to enumerate all of the various clinical phenomena which have been found to be associated with a state of hypoglycæmia. It is important, however, to emphasize that in many cases the neurological or psychiatric aspects of the condition are so prominent that many of the patients with chronic hypoglycæmia have been referred primarily to neurologists and psychiatrists for treatment. Sigwald refers to several recent reports of chronic psychoses in patients who were taking insulin which disappeared at once after the cessation of insulin treatment. It is interesting also that repeated observations have been made of hæmorrhages into the central nervous system in severe induced hypoglycæmia. This observation perhaps has a special bearing on one of our cases which will be noted later.

There is, of course, no definite level of the blood sugar at which the symptoms of hypoglycæmia are likely to appear. In general, however, the most severe manifestations are associated with the lowest findings of blood sugar. When the blood sugar diminishes to 50 milligrams or less per 100 cubic centimeters, the effects are likely to be severe.

Apparently the first suggestion of the possibility that the blood sugar might be excessively lowered spontaneously by an abnormal activity of the islet tissue of the pancreas was made by Seale Harris of Birmingham, Alabama, in 1924, in a paper entitled "Hyperinsulinism and Dysinsulinism." In this paper he reported 12 patients with blood sugar values of less than 70 milligrams, nearly all of whom presented many of the symptoms which have already been described as those associated with hypoglycæmia. Since one does not find such low blood sugar values in starvation, he concluded that probably they represented an expression of spontaneous hyperinsulinism. Jonas in the following year added another case in which, because the most striking symptoms were epileptiform, the patient was sent to an institution for epileptics and died there. This same case was later reported by Hartman.

The most striking evidence, however, of the occurrence of hyperinsulinism or dysinsulinism was presented in 1927 in the important report by Wilder, Allan, Power, and Robertson of their dramatic case. This concerned a man, 40 years old, who for more than 2 years had had attacks consisting of syncope, paræsthesia of the tongue and lips, asthenia, sweats, and trembling. These attacks occurred just before a meal or after unaccustomed exercise, and the patient had discovered that he could escape them by taking food or sweetened drinks. On one occasion he was comatose for a couple of hours and had been revived by injections of adrenalin and of dextrose. A sugar tolerance test showed a rise from 85 to 215 milligrams per cent at the end of a half hour and then a fall to 31 milligrams per cent three hours later. Finally it was calculated that this patient required as much as 25 grams of dextrose per hour to avoid his attacks. An exploratory operation by W. J. Mayo revealed a large nodular pancreas with metastatic tumors in the liver. From tissue recovered at autopsy a month later the tumor was found to be a primary carcinoma of the islands of Langerhans, and it was found to contain as much as 40 units of insulin to 100 grams of tumor. In the following year (1928) Thalhimer and Murphy

Fig. 1. Low power view of tumor with adjacent pancreas tissue. Note the lobulated appearance of the tumor and the tendency toward encapsulation. (Barnes Hospital, Case 2.)

reported the case of a woman 57 years of age with typical severe symptoms of hypoglycæmia in whom at postmorten examination there was found at the junction of the body with the tail a tumor of the pancreas 1.5 centimeters in diameter which was considered to be a carcinoma of islet tissue of low malignancy by the authors themselves as well as by Robertson, Wilder, and Bensley all of whom examined the sections. The tumor was well demarcated and was incompletely surrounded by a capsule of connective tissue. Nevertheless, it seemed to invade the surrounding pancreatic tissue.

The first successful operative removal of a pancreatic tumor producing symptoms and signs of hypoglycæmia was the case reported in 1929 by Howland, Campbell, Maltby, and Robinson of Toronto. This patient, 52 years of age, who had had symptoms of dysinsulinism for 6 years, had an encapsulated tumor in the body of the pancreas which was easily removable. The symptoms were completely relieved and the blood sugar was restored to a normal level. From the microscopic examination the authors considered this tumor to be a carcinoma.

The three cases just described were all thought to be carcinomata. There is now, however, good reason to think that benign adenomata of the islet tissue are capable of producing the characteristic clinical features of hypoglycæmia although there are some adenomata which are not accompanied by this condition. In 1926, Warren collected 16 cases of adenoma and added 4 more from his own study of autopsy material. Microscopically these tumors showed a resemblance to normal islet tissue in the arrangement and appearance of the cells, an absence of mitotic figures, by the presence of a definite capsule, and by compression of the contiguous pancreatic tissue. Apparently, however, none of these cases had been studied clinically with reference to the possible presence of evidence of hypoglycæmia. Lloyd, in 1929, reported a case of adenoma without hypoglycæmia found at autopsy, but this case was complicated by the presence of a tumor of the hypophysis and of the parathyroid glands. More recently Drs. Margaret Smith and Marshall Seibel of the department of pathology of Washington University have reported on 4 cases in which an adenoma was found at autopsy. In one of these cases hypoglycæmia was present but because the patient also had syphilis of the central nervous system the latter condition was thought sufficient to explain his mental symptoms. Accordingly, the presence of the pancreatic adenoma was unsuspected. In the second case in which the pancreatic adenoma was incidental to a primary carcinoma of the liver there had been no clinical evidence of hypoglycæmia, although no determinations of the blood sugar had been made. In the third case the autopsy had been performed by Dr. Rabinovitch at the Missouri Baptist Hospital on a man, 50 years of age, who had been operated upon for acute intestinal obstruction. No obstruction was found but instead a gall bladder filled with stones. Death occurred soon after the operation. No blood sugar analyses had been made. It is interesting, however, that subsequently it was learned from the family that the patient had been regarded as mentally defective for a number of years because of periods of loss of memory. The fourth case was a negress, 48 years old, who entered the Barnes Hospital with acute lobar pneumonia and with severe diabetes. Several days after the crisis sudden death occurred from a pulmonary embolus originating in a femoral vein. At the autopsy the pancreas was found to be smaller than normal. On the anterior surface of about the center of the body of the organ was a well encapsulated

Fig. 2.

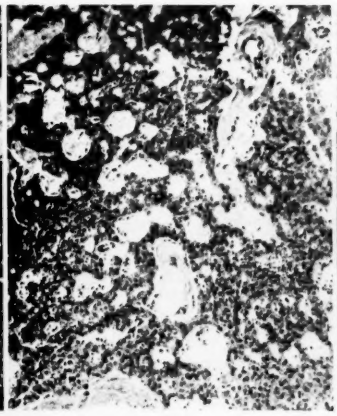

Fig. 3.

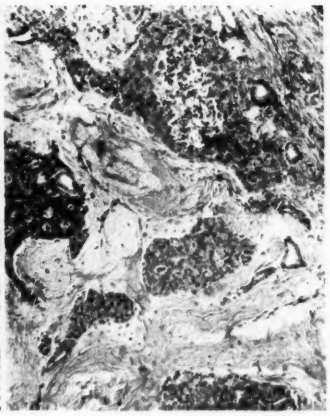

Fig. 4.

Fig. 2. Section taken through a very cellular portion of the tumor. Most of the cells seen are similar to the so called beta cells of the islands of Langerhans both in structure and function. (Barnes Hospital, Case 2.)

Fig. 3. Section which was taken through a more mature portion of the tumor. The appearance in this section is that of collagenous connective tissue. (Barnes Hospital, Case 2.)

Fig. 4. Connective tissue has become more abundant with an apparent disappearance of many of the tumor cells. This probably represents the oldest phase of the adenoma. (Barnes Hospital, Case 2.)

nodule which measured 1 centimeter in diameter. The authors, as well as Dr. Bensley who also examined the tissue, believe from the microscopic appearance that it is a true tumor and not merely a hypertrophic island. Because of their inability to demonstrate either alpha or beta granules in the cells it was decided that this was not an active tumor. Certainly there was no clinical evidence of activity because the patient had severe diabetes instead of hypoglycæmia. Thus of the 4 cases, one was definitely associated with hypoglycæmia, another had symptoms suggestive of it, a third had no clinical evidence of it but the amount of the blood sugar had not been determined, and in the fourth the patient had severe diabetes instead of hypoglycæmia.

In 1928, MacClenahan and Norris had reported their very definite case of adenoma associated with severe signs and symptoms of hypoglycæmia in a man 42 years old. At autopsy the tumor which was 1.6 centimeters in diameter was found to be plainly encapsulated. There were no mitotic figures and the cells for the most part resembled beta cells of normal islands. Neighboring pancreatic tissue showed some hypertrophied islands.

Since October, 1930, 3 patients have been successfully operated on at the Barnes Hospital for the removal of active tumors of islet tissue associated with marked evidence of hypoglycæmia.

The first case, which has been reported by Carr, Parker, Grove, Fisher, and Larimore, concerned a young man of 19, a student at a military school who was referred to the neurologic service of Dr. Carr by a physician who diagnosed the case as one of epilepsy because of repeated convulsive attacks which had been present for a year. It was noteworthy that these attacks occurred usually before breakfast. Under the strict discipline of a military school these attacks had been especially conspicuous, and even on occasions when there was no convulsive seizure the boy was often noted to act queerly while getting dressed and at the breakfast table. On several occasions he had been subjected to disciplinary measures. On one occasion he slept for 36 hours. At another time he drove an automobile in the streets of a large city, became involved in an accident, and had no recollection afterward of what had happened. When he recovered from the various attacks he was always ravenously hungry. Food, especially sweets, seemed to prevent the attacks. Blood taken during one of his attacks in the hospital showed only 44 milligrams of sugar per 100 cubic centimeters. A diagnosis of a probable islet tumor was made. Accordingly at operation on October 22, 1930, Dr. A. O. Fisher removed a well encapsulated adenoma from the upper, posterior

Fig. 5. Low power view of the tumor removed at the first operation. This was probably much older than the second tumor removed from the same patient later. See text for discussion of it. (Barnes Hospital, Case 3.)

border of the pancreas at about its midportion. The tumor was somewhat larger than most of those which have been described, measuring 2 centimeters in long diameter. The postoperative course was uneventful, the blood sugar was promptly restored to a normal level, and the patient's symptoms have been entirely relieved.

Our second operative case has also been separately reported. It concerned a farmer, aged 44 years, who had been in good health until October, 1929. One morning at this time he noticed that while doing his chores about the farm before breakfast he became mentally confused. He described the symptoms as similar to those of alcoholic intoxication. After eating breakfast he felt normal again. His next attack was early in the morning about 1 week later, when he noticed the same sort of feeling. Attacks began to be more frequent and a little more severe. Early in December, 1929, he had his first very severe attack, at which time he became unconscious and had to be carried into the house. He was given food and in a few moments was feeling normal again. His memory as to what took place during this seizure was considerably confused. He consulted his family physician, who could find nothing abnormal on physical examination. During the next 2 months the patient was examined at two different clinics, where the diagnosis of a possible brain tumor was made. He was given phenobarbital, with no improvement. He now began having attacks before rising in the morning, during which, according to his wife, he became much confused, spoke at random, and at times fell from his bed. She also noticed twitching movements, especially about the face. There were never any generalized convulsions. At another clinic it was found that he had a pathological condition of the gall bladder, and this organ was removed along with the appendix. There was no amelioration of the symptoms. It was at this time that his wife noticed that, if she fed him several times at night, his attacks could be prevented. He also began carrying candy around in his pockets during the day and noticed that frequent eating of it prevented the seizures. He was referred to us in January, 1931, for study. Drs. Womack and Gnagi had made a tentative diagnosis of an islet tumor on the basis of the patient's history before he entered the Barnes Hospital for study.

General physical examination gave entirely negative results. The blood pressure was 128 systolic and 74 diastolic. There were no positive neurological observations. The disks were normal, as were the visual fields. Roentgenograms of the skull were indeterminate. The basal metabolism rate was plus 3 per cent. The urine was normal; red blood cells 5,230,000, and white blood cells 6,600. The differential count was normal. Hæmoglobin was 90 per cent. The Wassermann and Kahn reactions of the blood were both negative. Phenolsulphonephthalein excretion was 80 per cent in 2 hours. The blood amylase determination by Elman's method was 7.5 units (5 units normal). Blood non-protein nitrogen was 27 milligrams per hundred cubic centimeters.

The patient was given his regular evening meal. This was followed by 200 cubic centimeters of milk at 7 p.m. and 200 cubic centimeters of sweetened grape juice at 9 p.m. He was not given any more food that evening. At 6:15 a.m. he was found to be awake. His face was expressionless, his pupils somewhat dilated and, though he answered when spoken to, his answers were incoherent. There was a generalized coarse tremor and the respirations were mildly Biot in character. A specimen of blood was taken for a sugar determination. The patient was then given 120 grams of dextrose by mouth (estimated weight 150 pounds or 68 kilograms). Ten minutes after receiving the dextrose he was again alert and did not remember any of the preceding events. No more food was given and blood specimens were taken at hourly intervals. At the end of 7 hours he again became slightly confused; he began to perspire; it was noted that the reflexes were slightly hyperactive. He soon presented the same clinical picture that he had presented earlier in the morning, and further food was given with immediate relief. The foregoing description is that of a fairly typical attack and was observed on several occasions.

The reaction to epinephrine was found to be a definite one. The patient was temporarily relieved of his confused state and showed at the same time a rise in blood sugar.

The reaction of pituitary extract was delayed and irregular, though there was a slight rise in blood sugar.

February 4, a laparotomy was performed (E.A. G.) The pancreas was exposed through the supra-

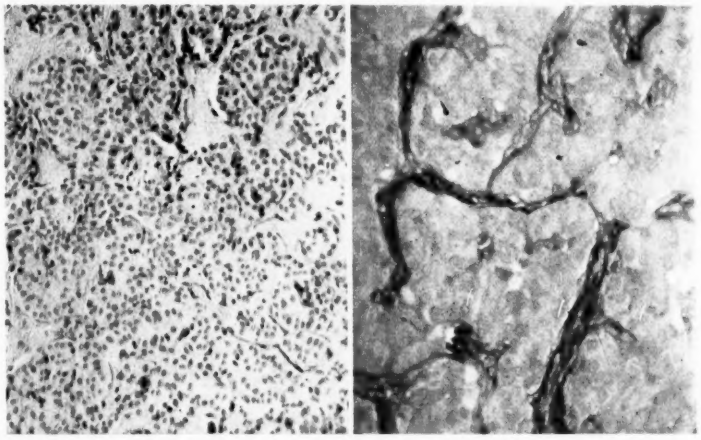

Fig. 6, left. Second tumor from same patient as Figure 5. Imperfectly formed lobules and sinuous cords of epithelioid cells. Hæmatoxylin and eosin stain. High power. (Barnes Hospital, Case 3.)

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colic omentum, and at about the junction of the body with the tail on the anterior surface a small tumor was seen, about one centimeter in diameter. It showed through the posterior peritoneum as a dark spot suggestive of a small hæmorrhagic area. It felt firm. When the peritoneum was incised it was found that the tumor could not be shelled out of the pancreatic tissue, and it was therefore necessary to dissect it out with a small margin of normal pancreatic tissue around it. Before this was done, a pursestring suture was placed in the substance of the pancreas in order to control hæmorrhage. The vessels in the region of the tumor were all enlarged. The edges of the tumor bed were brought together, and the peritoneum was then closed over. A small rubber drain was placed over this and brought out through the left side of the abdomen by means of a stab wound.

Convalescence was somewhat stormy at first. Immediately after the operation a pulmonary infection developed which, however, was not very severe. On the second day after operation there was a fairly rapid œdema of the lungs. The patient was placed in an oxygen tent and given atropine. His condition improved rapidly. A pancreatic fistula developed several days later. This did not cause any skin excoriation and was rapidly closing at the time he left the hospital. Since his operation he has not had any more attacks, although his diet has been one containing no more carbohydrate than that of a normal individual. Fasting for 12 hours has failed to bring on an attack. In fact, the blood sugar at this time was 99 milligrams per hundred cubic centimeters. At no time since operation has it been lower than this. We saw this patient again in December, 1932, nearly 2 years after his operation. He was in excellent health and he stated that he had had no further attacks of his former trouble.

We were fortunate in being able to submit the tumor tissue to Prof. R. R. Bensley of the University of Chicago, who was present at the time as a visiting professor of anatomy in Washington University. Dr. Bensley is recognized as an authority on the cytology of the pancreas. Excerpts from his report follow: "While examination of the fresh cells was in progress, another portion of the fresh material was stained with neutral red in a 1:10,000 concentration in physiological solution of sodium chloride. It should be remarked that, when normal islands of Langerhans are so treated, the minute granules which the cells contain stain rapidly a bright yellowish red color with the neutral red. The cells of the tumor showed, with the neutral red, a curious reaction, which was observed also in the case reported by Carr, Parker, Grove, Fisher, and Larimore. In that case the granules in groups of cells stained intensely with neutral red, while other groups of cells, clearly containing granules, failed to stain. Other cells of the same tumor showed scattered granules, staining with neutral red, dispersed among other granules which failed to stain.

"I was of the opinion when I examined this first tumor that the failure of the neutral red to stain every cell was due to the mechanical difficulty of penetration of the dye, but the examination of the present tumor, in which by the experience gained in the study of the first it was possible to take precautions to avoid this, indicates that in both tumors there are granules present which stain readily with neutral red and other granules which do not stain

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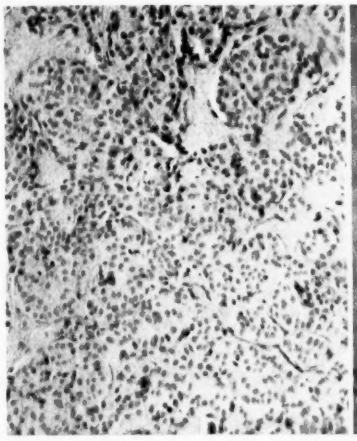

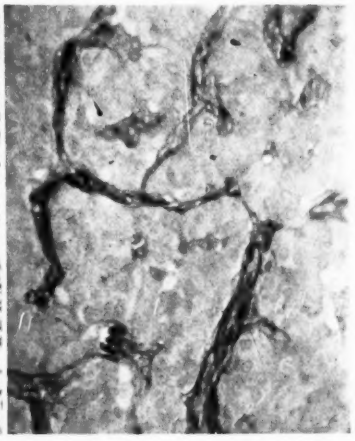

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"I was of the opinion when I examined this first tumor that the failure of the neutral red to stain every cell was due to the mechanical difficulty of penetration of the dye, but the examination of the present tumor, in which by the experience gained in the study of the first it was possible to take precautions to avoid this, indicates that in both tumors there are granules present which stain readily with neutral red and other granules which do not stain

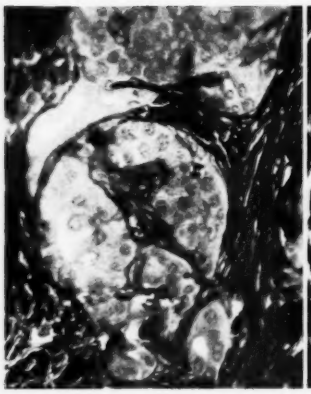

Fig. 8.

Fig. 9.

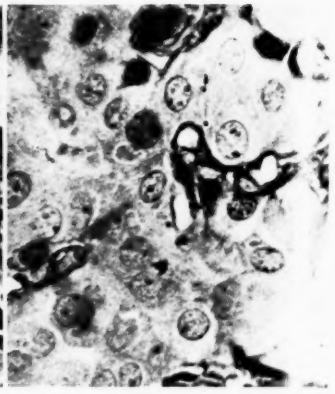

Fig. 10.

Fig. 8. The close approximation of the duct and islet tissue in the vicinity of the central core. (Barnes Hospital, Case 3.)

Fig. 9. Higher magnification of a portion of the same area as that seen in preceding figure. (Barnes Hospital, Case 3.)

Fig. 10. Cytoplasmic inclusions. (Barnes Hospital, Case 3.)

with neutral red. In the tumor now under description, scattered cells, not in groups, stained exactly as a normal beta cell of the islands of Langerhans stains; that is to say, the cells were packed with granules which stained brightly with neutral red. These cells did not occur in groups, as in the Carr, Parker, Grove, Fisher, Larimore case, but were individual. Many cells contained scattered neutral red stained granules mingled with granules of about equal size which refused to stain, but the majority of the cells contained granules which stained only faintly with neutral red.

"Two other observations were noted in all the cells of the tumor: a few granules, about the size of a zymogen granule, in the pancreatic acinus, more highly refractive than the regular granules and staining brightly with neutral red; a few cells contained rather indefinitely outlined amorphous bodies which stained rather faintly with neutral red. As the preparation became old, the cells behaved like island cells under similar circumstances; vacuoles formed in the cytoplasm, and the granules disappeared.

"The tumor was slightly irregular in outline and, as already mentioned, was not encapsulated. At portions of the surface it was separated by broad strands of collagenous connective tissue from the neighboring pancreatic lobules, but at other points it was actually in contact with pancreatic tissue, and at one point in the tumor the pancreatic acinus tissue was not only in contact with the tumor tissue but was actually in epithelial continuity with it.

"The substance of the tumor itself was imperfectly divided into lobular masses by heavy strands of collagenous connective tissue. In these bands, portions of pancreatic ducts were seen and, in addition, masses which presented the appearance found in lobules of a pancreas whose ducts have been ligated. In the latter masses, regenerated acinus cells, such as those which have been described by Grauer in his account of regeneration in the pancreas of the rabbit, were to be seen. There were also present in this tissue small and large groups of normal island cells, also probably of recent origin.

"The acinus cells seen in these complexes had evidently arisen by differentiation from duct epithelium, since they presented all grades of advance in the regenerative processes, as follows: (1) individual acinus cells surrounded on all sides by duct epithelium; (2) groups of two or three acinus cells, and (3) well individualized small acini. Ducts were in many places continuous with the epithelial masses of the tumor itself. The tumor tissue presented different aspects in its different parts, and these different aspects I conceive to be the different stages in the progress of this growth.

"One lobe separated from the others by strands of connective tissue presented the appearance of an enormous, overgrown island of Langerhans, except, as appeared later, for the fact that the cells which composed it were not normal island cells of either category but abnormal tumor cells of island reference. This portion of the tumor consisted of anastomosing cords of epithelial cells separated by wide sinusoidal capillaries, the endothelium of which was almost in contact with the epithelial groups, a minimum of reticular connective tissue being interposed.

"In the adjacent portion of the tumor the proliferation of the epithelial elements had exceeded the rate of growth of the vascular components, and in this portion of the tumor an extraordinarily large mass of epithelium was traversed only by a normal number of capillary blood vessels, and these showed a tendency to become separated from the epithelial elements by an increase in the layer of connective

tissue outside of the endothelial tube. In some of these cellular masses there was a breakdown of cells, forming spaces containing scattered necrotic epithelial cells and much blood, the blood vessels having evidently ruptured into the space provided by the death and dissolution of the epithelial cells.

"In the third section of the tumor an appearance which approached that in the Carr, Parker, Grove, Fisher, Larimore case was attained. Groups of epithelial cells were separated from one another by wide strands of hyalinized connective tissue containing blood vessels. Degenerative processes in this tumor were not nearly so manifest as in the tumor removed by Dr. Fisher, but in places the cells had completely broken down and the place formerly occupied by them was now filled with blood, a few scattered epithelial cells and, in some instances, isolated groups of tumor cells attached to the walls.

"Sections of material fixed in chrome sublimate and in formol-Zenker, stained with Bowie's stain or Bensley's neutral gentian, revealed the fact that only a small proportion of the cells of the tumor had the characteristics of normal beta cells.

"Examination of the material fixed in chrome sublimate or formol-Zenker, stained with neutral gentian or with Bowie's stain, showed that many cells in this tumor contain beta granules associated with granules of another sort. This observation recalls that made by Robinson, that in his tumor some cells contained both alpha and beta granules.

"The cytologic study of this and of the preceding tumor, and of the one reported by Robinson, indicates that in this case the tumor is not one composed of normal island cells but, on the contrary, one composed of cells which, while having a considerable resemblance to island cells, yet differ from them in important details. These differences consist of the production of a granular secretion antecedent, which differs in important details from the normal content of the island cells, and in the presence in these cells of a chromophil substance, unusual to island cells and found in normal pancreas only in acinus cells.

"The normal pancreas, as is well known, contains a very considerable excess of island tissue and yet ordinarily does not yield to the general circulation an excess of insulin. The fact that a tumor of such meager proportions could produce the symptoms of insulin shock and yet not be responsive as the normal islands are to the mechanisms that ordinarily regulate the export of insulin from the pancreas, is possibly to be found in the fact that the lesion under discussion is an abnormal cell type which, to be sure, resembles island cells but is not identical with them.

"Some doubt exists in my mind as to whether this tumor should be regarded as adenoma or carcinoma. The failure to form a definite capsule and the inclusion of normal pancreatic elements in the tumor itself seem to favor the latter diagnosis."

Our third and last case presents the unique feature of having two tumors and two operations for their removal with a final successful outcome. This case has not been reported elsewhere.

A young man, aged 22 years, of Jewish extraction, was first admitted to the Barnes Hospital on March 14, 1928, on the neurological service for the diagnosis of epilepsy.

He had had tuberculosis of the hip at the age of 3 for which he wore casts and braces until the age of 13; scarlet fever at the age of 15. In 1926, at the age of 20 he graduated from the St. Louis School of Pharmacy apparently a fairly capable student and since then has been working as a druggist.

In March, 1927, he noticed twitching in his legs after walking a few blocks. This occurred particularly at the end of his day's work when walking home from his drug store which usually occurred just before dinner. After dinner he could walk a much longer distance without observing any twitching of his legs. In January, 1928, he noticed a similar twitching of his arms just before dinner and with this there was a feeling of "drawing of his face" associated with pallor and sweating. On one occasion he stared straight ahead for a minute or two and after being put to bed made an immediate recovery from these symptoms. In February, 1928, he had several fairly typical attacks of petit mal which lasted from 3 to 5 minutes. There were no after effects but often there was a feeling of nervousness and weakness just preceding the attacks.

Upon admission to the hospital the patient was found to be intelligent and co-operative. His memory was good and he appeared to be interested in the examination, appearing neither depressed or excited. There was a slight slurring of speech and occasional twitching movements of various muscle groups. His gait was what was to be expected from the ankylosis of the left hip with a scoliosis. The blood pressure was 110–60, the pulse 70. A nystagmus was present and a discharge from the right ear, apparently from a chronic mastoiditis. No blood sugar determination or blood chemistry was done. All the routine laboratory work, including a blood Wassermann, was negative. The patient was considered atypical of epilepsy and was discharged for further observation.

Three months later he was readmitted to the hospital with no apparent change in his condition. At this time a tonsillectomy was performed.

On January 30, 1931, the patient was readmitted to the hospital. During the past year the attacks had become more frequent and more severe. Examination at this time showed him to be still intelligent and co-operative. No blood chemistry determinations were made because of certain observations by the psychiatrist who was taking care of him at this time and who thought his condition to be due to sexual repressions. He was treated by psychoanalysis and hypnotism with no apparent improvement.

On August 8, 1931, he was again admitted to the hospital and on questioning him at this time the patient gave only nonsensical answers. His attacks continued to be severe. No additional positive findings were noted on examination.

On May 9, 1932, he was readmitted to the hospital for the fifth time. He had now begun to have several attacks a day of petit mal. There was also a progressive muscular weakness. He entered the hospital during one of his attacks of petit mal. A sample of blood was taken immediately and the sugar was found to be only 25 milligrams per hundred cubic centimeters. The blood calcium was 5.5 and the phosphorus 10.6. He was given 50 cubic centimeters of 50 per cent glucose intravenously immediately. After receiving the first 25 cubic centimeters he aroused and was able to answer questions. When all of the 50 cubic centimeters had been received he was able to sit up and talk intelligently. His memory of the attack was poor. He had entered the hospital in the evening and after receiving the intravenous glucose he was given sweetened fruit juices to drink. On the following morning at 5 o'clock he had another seizure which disappeared 10 minutes after drinking a glass of orange juice.

On May 11, carbon dioxide combining power of blood was 73.51 per cent; calcium 10.9 milligrams per cent; phosphorus 3.6 milligrams per cent.

A sugar tolerance test was performed with the following result:

	Milligrams per cent
7:45 a.m. fasting blood sugar	58
8:12 a.m. glucose	
8:40 a.m.	112
9:10 a.m.	133
10:10 a.m.	117
11:10 a.m.	60
12:10 p.m.	53
1:10 p.m.	43
2:10 p.m.	40

Urine collected from 8:40 a.m. to 11:10 a.m. negative for sugar.

On May 13, the patient was found by Miss Kendall to have an intelligence quotient of 60. Her conclusions state, "this is evidently not representative of patient's original intellectual endowment. Scattered distribution of success and failure, the relatively high vocabulary and the difficult co-operation would indicate this even if the history were not known. Objective findings, Stanford: lowest failures all in reversing digits and in making sentences to include three given words (9 years). The best work in inductive reasoning (14 years) and in vocabulary (12 years)."[1]

On May 19, after receiving 500 cubic centimeters of 10 per cent glucose intravenously a laparotomy was performed (E.A.G.). An upper left paramedian incision was made and the pancreas was exposed through the gastrohepatic omentum. A small hard tumor was immediately felt and seen on the anterior surface of the pancreas at about the junction of the left and middle thirds. The tumor was clearly exposed and was seen to project slightly forward. One portion of it was so hard that it suggested calcification. There was a slight bluish discoloration of the tumor which made it distinct in appearance from the rest of the pancreas. A pursestring suture of catgut was placed around the tumor bed and the tumor removed. This was easily accomplished and there was only one small vessel at the pedicle. It was not necessary to remove any appreciable part of the normal pancreatic tissue. When removed the tumor was found to be about 1 by 0.8 cubic centimeters. It was immediately placed in fixing fluid, a rubber dam drain was inserted down to the pancreas and the wound was closed in layers. The operation was prolonged because of frequent attacks of apnœa. The anæsthesia used was nitrous oxide-oxygen with a little ether.

At 11 a.m. (immediately following the operation), the blood sugar was 190 milligrams per cent. Five hundred cubic centimeters of 10 per cent glucose were given intravenously followed by 2,000 cubic centimeters of physiological saline solution subcutaneously.

At 2 p.m. the blood sugar was 212 milligrams per cent; 4 p.m. the blood sugar was 170 milligrams per cent.

May 20, 9 a.m., the blood sugar was 122 milligrams per cent, no convulsions had occurred, 500 cubic centimeters of 10 per cent glucose were given intravenously.

May 21, 9 a.m., the blood sugar was 96 milligrams per cent (fasting). Five hundred cubic centimeters 10 per cent glucose given intravenously.

May 23, 9 a.m., blood sugar 102 milligrams per cent (fasting). Blood calcium 9.6. Blood phosphorus 2.9. Later in the day he had a convulsion, the first since his operation. He was given some fruit juices during the day by nasal tube.

May 24, 9 a.m., blood sugar 34 milligrams per cent (fasting). Carbon dioxide combining power 69.7 volumes per cent. The patient had another convulsion which was controlled by the drinking of fruit juice.

From then on during the next few days the patient was given large amounts of carbohydrates until on May 28 he was receiving 600 grams of carbohydrate per 24 hours. Although there had been no convulsions since May 24 the patient had been apathetic, incontinent, with hyperactive reflexes and a peculiar muscular rigidity associated with carpal spasm suggestive of tetany. This latter phenomenon had been noted before the operation but it had never been associated with an abnormally low blood calcium. The patient now developed an extreme mental confusion. On June 7, a note was made that the electrocardiographic record showed simple tachycardia. Roentgenogram showed normal sella. No changes in

[1] The diagnosis of a probable pancreatic tumor and the suggestion to perform the operation were made by Drs. Barr, Alexander, Schwab, Parker, Grove and others.

eye grounds. A previous examination of the visual fields gave normal findings. The blood pressure readings were always practically normal.

From this time on, in spite of large amounts of carbohydrate, the patient's condition became steadily worse. On June 25, the note was made that he was stuporous although responding slightly to cutaneous stimuli. There was slight cyanosis and the respirations were only 5 per minute. This recalled the periods of apnœa noticed at the operation. There had been no convulsions during the last few days but there was bilateral ankle clonus and slight rigidity of the left lower extremity. Because of a suggestion made in the report of Wilder et al. that perhaps ether anæsthesia increased the blood sugar and in view of the temporary improvement noticed in our patient after the operation it was decided to subject him to an ether anæsthesia. At the beginning of the anæsthesia which was at the end of a 7 hour fast his blood sugar was 40 milligrams per cent. At the end of 50 minutes of anæsthesia his blood sugar was 45 milligrams per cent and 1 hour later it was 54 per cent. Three hours later, however, while still fasting the blood sugar had fallen to 22 milligrams per cent. During the next few days, in spite of high carbohydrate feeding, convulsions were frequent and the patient became increasingly worse. Tests to demonstrate insulin in the urine made by Dr. Kuoymann of the department of biochemistry uniformly were negative, concentrated urine, ammonium sulphate precipitation, and alcoholic extraction being used.

Because it was felt that we had failed to find the active tumor responsible for the patient's condition, especially in view of the results of the microscopic examination of the tumor which had been removed, which will be described later, the question of operating on the patient again was discussed. It was felt that unless another operation revealed an active tumor the patient would almost certainly die and that therefore another operation was plainly indicated. Accordingly on July 14, 1932, after the patient had been given 500 cubic centimeters of 20 per cent glucose intravenously the abdomen was reopened through an incision just to the left of the former incision and the pancreas was exposed again all along the anterior surface through the gastrohepatic omentum. Nothing resembling a tumor was found on the anterior surface. The tail was then mobilized and rotated forward. Within the substance of the tail, but not visible on the surface, a nodule was felt which was firmer than the rest of the pancreatic tissue. This could be felt only by palpation of the organ between the thumb and index finger. It was closer to the posterior than to the anterior surface. It was about 2 centimeters in long diameter. It was removed together with about 4 centimeters of the tail. In cutting through the nodule after its removal a rather homogeneous appearance was noted on cross section which made it seem certain that the nodule was composed of tumor tissue. The remainder of the organ was examined as far toward the head as possible but no evidence of other tumors was found. Both adrenal glands were felt and found to be of normal size. The liver appeared to be normal but a small piece was removed for microscopic examination which was later found to be normal. The stump of the pancreas was closed over itself with chromic catgut. Immediately after the operation the blood sugar was 235 milligrams per cent. Another intravenous injection of 500 cubic centimeters 10 per cent glucose was given. Ten hours later the blood sugar was 218 milligrams per cent.

From then on the blood sugar remained normal or slightly above normal. On July 18, it was necessary to open the wound slightly to give access to about 50 cubic centimeters of pus which seemed to come from around the pancreas. Except for this complication the postoperative course was uneventful.

On August 9 a note by Dr. A. B. Jones states that there is definite evidence of extrapyramidal tract degeneration.

The patient was discharged on September 14. He had shown very marked and steady improvement since the second operation and there had been no convulsions.

On October 17, he was readmitted to the hospital for observation. His sugar tolerance showed a slight tendency toward diabetes. There had been steady improvement in the patient's mentality and another examination by Miss Kendall at this time showed an intelligence quotient of 71 as compared with 60 on the preceding examination and a gain of 22 months in mental age. The patient was actively interested in everything going on around him and was able to defeat his father and his brother in chess. He was still unable to walk but a very definite improvement in muscle tonus was observed. Some of his difficulty in walking was undoubtedly due to the ankylosis of his hip joint which was noted in the first examination.

It is still uncertain how much additional improvement will occur in this patient's mentality. It seems probable that his central nervous system was more or less permanently damaged by allowing a condition of severe hypoglycæmia to continue for too long a time.

Examination of the tumors. The two tumors removed from this patient were examined by Professor Bensley as well as by Dr. O'Leary of our department of anatomy, a former pupil of Bensley's. An abstract of Dr. O'Leary's report which includes both his and Dr. Bensley's opinions follows:

"The first tumor measured approximately 1.0 by 0.8 cubic centimeter and was composed of purple red friable tissue surrounding a heavily calcified core. Examination of the fresh material revealed a predominance of lymphocytes, with numerous histocytes, less numerous polymorphonuclears and eosinophiles. In histological section this mass resembled a calcified lymph node with hyalinization. Dr. Bensley, to whom the sections were sent to rule out

finally the presence of islet tissue, felt that the specimen was a badly sclerosed lymphatic gland with a considerable amount of active reticular tissue proliferation. However, it was removed from the substance of the pancreas and its great similarity to the pocket of tissue found in the capsule of the second tumor, both in gross and microscopic appearance, suggests the possibility that it might at one time have been an active tumor which became atrophied and was completely replaced when the present tumor arose. Supporting this possibility is the extension over a period of 3 years and the finding of a relatively young tumor mass at the last operation.

"The second tumor consisted of an ovoid mass, 2.0 by 1.4 by 1.2 cubic centimeters, of firm elastic consistency. No hæmorrhagic or necrotic areas were visible, but embedded in the capsule was a single nodule of friable purple red tissue, 3 millimeters in diameter. This nodule consisted chiefly of lymphocytes with numerous macrophages and fibroblasts, less numerous polymorphonuclears and eosinophiles. It resembled in structure the first tumor which was removed from the same patient." As the result of an extensive study of the whole tumor after the use of various fixing agents and stains Dr. O'Leary summarizes his examination as follows: "the findings support the conclusion that the tumor removed was an adenoma of the islet type, cytologically very similar to those previously studied by Bensley and others; but due to its size and excellent accommodation of tumor growth to vascular supply, it was capable of producing relatively more of the hypoglycæmic hormone than the previous tumors studied at this institution. In making this diagnosis, questionable evidence of malignancy has been discounted. The deviation of the majority of tumor cells from the beta type gives further affirmation to the 'dysinsulinism' hypothesis."

The detailed report of the second tumor follows:

"When cut, it appeared homogeneous throughout, save for strands of fibrous tissue traversing it. No hæmorrhagic or necrotic areas were visible. Embedded in the capsule, however, was a single nodule of friable tissue purple red in color and 3 millimeters in diameter. This was dissected free and placed in Ringer's fluid for examination in the fresh. A sagittal block, including tumor tissue and adherent pancreas, was fixed immediately in formol chrome sublimate. Successive slices toward one surface were fixed in aqueous and acetic chrome sublimates, Altmann's and Bouin's fluids and formol absolute alcohol (the latter for micro-incineration). At the same time small bits were preserved in Ringer's fluid and in 0.1 and 0.05 per cent neutral red (Gruebler No. 0529) in normal saline. These bits provided material for the examination of fresh tissue. The remainder of the tumor was set aside for physiological assay.

"The bits of tissue for fresh examination teased with difficulty. Cells did not float free as in the Womack et al. and Carr et al. tumors previously studied by R. R. Bensley. Even so, groups of cylindrical and polyhedral cells having clear nuclei, prominent nucleoli, their cytoplasm occupied by a haze of tiny granules, could be easily differentiated. To one familiar with the appearance of living islet cells of the pancreas this evidence was almost conclusive that the parenchyma of the tumor consisted of cells closely allied to this type. Prominent canals of Holmgren and refractile droplets could also be distinguished in some of the cells. In the material immersed in neutral red, the granules of but occasional cells colored the characteristic brick red that identifies beta islet cells. That this was not due to mechanical factors is illustrated by the occurrence of these cells among groups of cells whose granules remained uncolored. As compared with the Womack et al. and Carr et al. tumors, the cells whose granules colored by neutral red appeared to be significantly less numerous.

"The reddish friable mass removed from one wall of the tumor had a cell content identical with that observed in a preceding mass removed from the pancreas of the same patient: it consisted predominantly of lymphocytes with numerous macrophages and fibroblasts, less numerous polymorphonuclears and eosinophiles. The possible significance of this finding will be discussed later.

"The fixed tissue was sectioned in paraffin at 4 μ. The slice through the center of the tumor (formol chrome sublimate fixation) well illustrated the condition that maintained in all but isolated portions of the tumor. Sections from this and other blocks were colored by Mallory's triple stain, the Heidenhain azocarmine modification of the same, Bensley's and Bowie's neutral stains, hematoxylin and eosin and Delafeld's hematoxylin followed by Giemsa's eosin azure. The neutral dyes of Bensley and Bowie, which facilitate the identification of cell types in islet tissue, and the azocarmine modification of Mallory's connective tissue stain proved to be the most useful.

"When a Mallory slide of the central block was examined, it immediately became apparent that the major portion of the tissue closely resembled the 'beginning tumor stage' (classification by Bensley, Womack et al.) of islet cell adenomata, and was remarkably similar to Robinson's description of the condition that prevailed in a tumor of the same type reported by Howland et al. It has a well developed stroma of collagenic connective tissue. Capillaries which issued from the arteries of this framework, carrying with them occasional collagenic fibrils, imperfectly divided the parenchyma into lobules and sinous cords of epithelioid cells, two to several cell layers in thickness. Figures 6 and 7 illustrate this condition. There was in addition a dense central core of connective tissue and several lesser ones. These contained, besides arteries and veins, ducts of medium to small size and islets of tumor tissue. In the more superficial portions of the fixed material (aqueous and acetic chrome sublimate blocks) the connective tissue was richer in areas than in the

central block, but, as elsewhere, no hyalinization had occurred. Surrounding the tumor was a broken capsule.

"Ducts were not of frequent occurrence throughout the tumor. In the central block, medium to small sized ones were found in the accumulations of connective tissue and at the surface of the tumor approximating the pancreas. From the connective tissue accumulations the ducts, as well as tongues of islet tissue, might be seen to project into the surrounding parenchyma. Figure 8 is a photomicrograph showing the close approximation of duct and islet tissue in the vicinity of the central core. Figure 9 is a higher magnification of the same area. In the region adjacent to the pancreas (central block, formol chrome sublimate) the connective tissue partition separating pancreas and tumor was broken by the egress of the ducts. The ducts in this area were differentiating into both islet and acinar cells. All the stages in the differentiation of acinar tissue were there to be observed. In the more superficial blocks of the tumor the capsule between pancreas and tumor was broken and normal pancreas graded into an area of regenerating (?) pancreas, this in turn into tumor. In these blocks, ducts were much more numerous throughout the parenchyma and stages in their differentiation into islet cells were apparent.

"The parenchymatous cells of the tumor could be readily recognized as closely akin to the islet variety. Their shape variations were similar; they were, however, most frequently larger in size as compared to normal control islets of the same section. The cytoplasmic granules of occasional cells gave staining reactions identical with those of the beta variety of islet cells. More often in these cells the granules were packed uniformly with the exception of the area occupied by the canals of Holmgren, but in some they appeared to be concentrated at the capillary pole. The cytoplasmic granules of the predominant majority of the tumor cells (henceforth called 'tumor cells' to differentiate them from the beta cells of the tumor) stained differently, but digression is necessary to explain the effect of coloring with neutral dyes. With Bowie's stain (formol chrome sublimate fixation) scarcely differentiated in absolute alcohol, the beta cell granules stained deep blue, the tumor cell granules lilac. Slightly better differentiated, the beta cell granules were a lesser blue, the tumor cell granules pink. This transition in colors due to different degrees of differentiation was not so noticeable with Bensley's neutral gentian and here the beta cell granules stained deep purple, the tumor cell granules a lighter purple. Tumor cell granules were less closely packed in the cytoplasm, the canals of Holmgren could not always be distinguished, and the small vacuoles occasionally seen in the cytoplasm of beta cells were lacking. Only one cell was observed in the tumor whose granules gave the staining reactions of those characteristic of the normal alpha cells of the islets of Langerhans.

"Cytoplasmic inclusions of varying shape but identical staining reactions were observed in tumor islet cells. Presumably these were identical with the chromophile material described by Bensley as occurring in the islet cells of all the tumors that he studied. They might be plastered on the outer surface of the nucleus (sickle thickening of Bensley) or occur as discrete bodies in the cytoplasmic mass. The latter were round or spiroid in appearance. Observed in a mitotically active cell, they colored the same as the chromosome mass and could only be distinguished from it by a knowledge of their appearance in resting cells. Dr. G. H. Scott informs me that in micro-incinerated sections these inclusions gave evidence of the presence of iron. They did not occur in the cytoplasm of the cells which contained degenerating nuclei. Several typical ones are illustrated in the accompanying photomicrograph Figure 10.

"About the margins of the tumor, nuclear pyknosis was to be observed. Other evidence of nuclear degeneration also occurred in the body of the tumor. Single cells or patches might be thus affected. Significant of this change was the appearance of clumps of chromatin within the nucleus. All stages between this and complete pyknosis were found. The cytoplasm of cells whose nuclei were thus affected became basophilic and discrete cytoplasmic granules could no longer be distinguished. Cells with hyperchromatic nuclei and those with mitotic figures were infrequently met with. In the cytoplasm of the latter, the specific granules of 'tumor cells,' though they were reduced in number, could be distinguished. Mitotic figures were not observed in beta cells of the tumor.

"The tumor parenchyma gave a negative Masson reaction for argentaffine cells. After 24 hours, staining of the granules of histocytes could be observed, but the islet cells were free from silver deposit. A control slide of Bouin's fixed intestine showed excellent argentaffine cells."

Insulin assay of second tumor (*Dr. Kuoymann*). A portion of the tumor weighing 0.582 gram was treated according to the method which was found by Best and Jepthcott to give the maximum yields of insulin.

The extract was made up to 25 cubic centimeters in a volumetric flask and 10 cubic centimeters were injected into the marginal ear vein of a rabbit. Blood samples taken at various intervals gave the following results:

	Milligrams per cent
Initial blood sugar	114
½ hour	92
1 hour	54
2 hours	52

Calculated by the method of Freudenburg the injected extract contained approximately 0.9 rabbit units of insulin.

A second rabbit was given 12 cubic centimeters of

the extract intraperitoneally. The blood sugar values were as follows:

	Milligrams per cent
Initial blood sugar	117
1 hour	86
2 hours	82
3 hours	46

3¼ hours. Convulsions appeared that were relieved by glucose. The tissue analysed therefore contained approximately 4.0 rabbit units of insulin per gram of tissue. This is 10 times the amount of insulin found in the carcinoma of the islets in the case of Wilder, Allan, Power, and Robertson.

This last case not only differs from any of those previously reported in that two tumors were present for the removal of which two operations were performed but there were several other unique features. For example, this is the first case in which a tumor was removed which was embedded in the substance of the organ and detected only by palpation instead of by vision; it happened that the second tumor in this case could be found only by palpation. Again, it seems surprising that in spite of the evidence of marked activity of this tumor no insulin could be demonstrated in the urine. This is perhaps the more astonishing since the assay of the tumor tissue revealed as much as 4 rabbit units of insulin per gram of tumor tissue, ten times as much as the amount found in the carcinoma of the islets reported by Wilder, Allan, Power, and Robertson. Finally also, it seems possible that some of the changes in the central nervous system in this case are of a permanent nature which may have resulted from allowing the severe hypoglycæmia to continue for too long a time, or perhaps they may be the result of hæmorrhages which are known to occur sometimes in of severe hypoglycæmia.

Including one case mentioned by Cushing as having been operated on at the Peter Bent Brigham Hospital but concerning which no details have been presented, this last case of ours is the fifth one from which a tumor has been successfully removed. Of these 5 cases 3 have been at the Barnes Hospital. It is an interesting fact that in the 4 cases about which the details have been published there has been no mortality. The absence of mortality and the uniformly dramatic nature of the recoveries constitute an effective plea for more prompt surgical exploration in cases of hypoglycæmia of unexplained origin.

Unfortunately, the diagnosis of the presence of an islet tumor is by no means easy. The recognition of a state of chronic hypoglycæmia even with the characteristic symptoms of the condition is not sufficient evidence in itself upon which to make a diagnosis of an islet tumor. Thus, for example, other conditions have been found to be associated with the hypoglycæmic state. Phillips, in 1931, reported a case presenting symptoms of severe hypoglycæmia even with loss of consciousness. One determination of the blood sugar was as low as 25. At autopsy, in addition to a subacute glomerular nephritis, the islands of Langerhans were found to be markedly hypertrophied (242 to 328 microns as compared with the normal figures given by MacCallum of 146 to 157 microns). It is well known that disturbances of the adrenal glands may be associated with hypoglycæmia. There are now on record many observations showing that the blood sugar is lowered in Addison's disease, and Anderson has reported a case in which there were pronounced symptoms of hypoglycæmia associated with a carcinoma of one adrenal gland. Again also, the condition of hypoglycæmia is sometimes associated with certain tumors of the pituitary, especially those which arise in the chromophobe cells which manifest adipose-genital symptoms of hypopituitarism. The literature on the association of pituitary lesions with hypoglycæmia is extensively reviewed in Sigwald's monograph. Various diseases of the liver, such as primary carcinoma, (5, 19), neoarsphenamine hepatitis (6) and phosphorus poisoning, as well as such a condition as scleroderma (4), are known to be associated with hypoglycæmia. Again, other cases, especially in children, have been noted in which a clinical picture closely resembling that of an islet tumor has been present but has disappeared spontaneously. Several such cases have been observed at the St. Louis Children's Hospital. For example,

M. R., aged 2 years, had been caught by his mother stealing jam and jelly from her cupboard. The small boy was disciplined and the desired sweets were moved to a more secure place which was inac-

cessible to the pilfering fingers. On the morning of the second day after the event his mother found it difficult to arouse him. He was brought to the Children's Hospital (September 3, 1931) where he was found to be in coma, with vomiting and acidosis. His blood sugar at the time was only 20 milligrams per cent. He was revived immediately by an intravenous injection of glucose. A sugar tolerance determination on September 5 showed:

Fasting	.077
½ hour	.112
1 hour	.104
2 hours	.109
3 hours	.090

Although observed repeatedly since his discharge he has been entirely normal. An operation on his pancreas at the time would have been ill advised. But yet one wonders what the future may show in regard to this child.

It is therefore apparent that the diagnosis of a state of spontaneous hypoglycæmia does not in itself establish the diagnosis of an islet tumor. Moreover, it will not always be easy for the surgeon to recognize the tumor even when present. If, for example, it should happen to be embedded in the substance of the pancreas its recognition might be impossible by any justifiable means. Again, our last case complicates the situation still more because of the demonstration of more than one tumor, a feature which adds an aspect of a possible therapeutic incompleteness if only one tumor has been found and removed. Finally also it would seem now as if sometimes adenomata are present which are inactive. However, if an adenoma is found in a patient who has hypoglycæmia the chances are very great that the removal of the adenoma will be followed by a marked improvement in the patient's condition.

Several failures to find a tumor at operation in clinically typical cases have now been recorded. In some of these cases attempts to correct the hypothetical condition of hyperinsulinism have been made by the removal of a large part of the pancreas. Such attempts have been made by the Finneys, by Holman and by Allan, Boeck and Judd. The results in these cases have been disappointing. Perhaps an active tumor was overlooked and allowed to remain. Moreover, it is hardly to be expected that the removal of anything less than nearly all of the pancreas would accomplish a desired result in correcting the hypoglycæmia unless by the removal of a part of the organ an active tumor was inadvertently extirpated. Recently, however, Seale Harris has informed us in a letter of a case of "narcolepsy that was operated upon by Dr. Adrian Taylor for me, and the patient was cured clinically by the resection of about half the body and all the tail of the pancreas except the portion attached to the splenic vessels."

Note.—Since the preparation of this manuscript information has reached us that 2 additional cases of islet tumor have been successfully operated upon, one by Schmidt at the University of Wisconsin Hospital and one by Ross and Tomasch at the Cleveland City Hospital. These 2 cases bring the number of the total of successful cases of removal of an adenoma to 7, with no reported mortality.

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STUDIES ON TUMOR METASTASIS

I. DISTRIBUTION OF METASTASES IN CARCINOMA OF THE CERVIX UTERI

SHIELDS WARREN, M.D., BOSTON
From the Laboratories of Pathology of the New England Deaconess Hospital and of the Harvard Cancer Commission

THE distribution of metastases has been studied in a series of 1,059 autopsies on cases of malignant disease taken from the files of the Huntington Memorial Hospital from 1914 to date, from the Department of Pathology of the Harvard Medical School from 1920 to date, from the House of the Good Samaritan from 1920 to date, from the New England Deaconess and Palmer Memorial Hospitals from 1928 to date, and from the Pondville Hospital from 1928 to date.

Only those autopsy protocols were utilized which afforded a satisfactory gross description and at least a fair clinical history. No case was included without review of the microscopic slides. For the statistical compilation of much of the data, which was facilitated by the use of the punch card system, I am indebted to Dr. Herbert L. Lombard, director of the Division of Adult Hygiene of the Massachusetts State Department of Public Health, and his assistants.

TABLE I.—TYPES OF TREATMENT OF 132 CASES OF CARCINOMA OF CERVIX UTERI AS DETERMINED AT AUTOPSY

Type	Number	No or palliative treatment	Operation	Radon	X-ray	Combined	Average total duration, years
Epidermoid I	25	6	7	9	..	3	2.5
Epidermoid II	66	11	7	29	2	17	1.9
Epidermoid III	21	3	..	12	..	6	1.3
Epidermoid not stated	4	1	..	1	..	2	0.8
Adeno-acanthoma	5	1	..	2	..	2	2.0
Adenocarcinoma	11	1	1	7	..	2	2.0

TABLE II.—DISTRIBUTION OF METASTASES

Type	Number	No metastases		Metastases to				
		Number	Per cent	Regional nodes	Distant nodes	Lungs	Liver	Bone
Epidermoid I	25	15	60	10	7	..	1	
Epidermoid II	66	17	26	46	31	8	15	3
Epidermoid III	21	3	14	17	17	9	9	2
Epidermoid not stated	4	4	100	..	..	..	..	..
Adeno-acanthoma	5	..	..	5	2	1	1	
Adenocarcinoma	11	1	9	6	6	2	2	

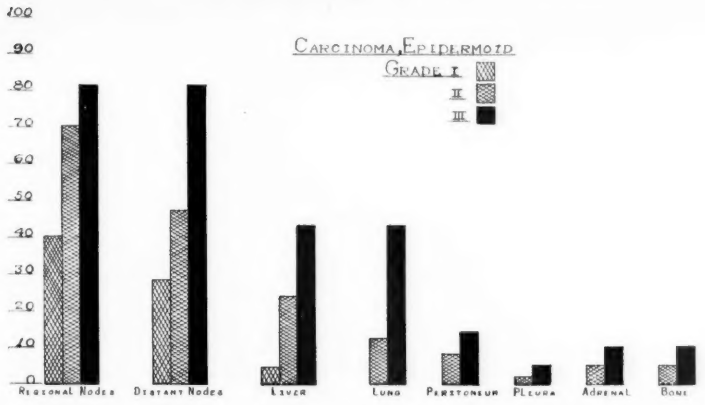

Fig. 1. Graph showing percentage of distribution of metastases.

In this series of 1,059 cases are included not only so called active cases of cancer but a large number of terminal care cases as well. Many of the patients were treated, others were untreated, so an opportunity was afforded to study the behavior of untreated cancer as well as the treated forms of the disease.

Among this group were 132 cases of carcinoma of the cervix uteri.

In Table I is shown the distribution of these cases by histological class and the type of treatment given them. The cases which had no palliative treatment represent those coming to the hospital with far advanced disease, or those who for religious or other reasons refused treatment of any sort. Under the heading of palliative treatment are grouped those cases in which the patients received small doses of deep X-ray, colostomy for intestinal obstruction due to the presence of the tumor, or other treatment instituted only with the idea of symptomatic relief and not expected to lead to cure or to appreciable amelioration of the disease. It is rather striking evidence of the delay in seeking treatment that 23 of these patients were found, 17 per cent of the total.

Of course many additional patients given intensive treatment had well advanced growths when treated. Thus Leland found among 711 traced cases of cancer of the cervix, treated with radium at the Huntington Hospital, that only about 10 per cent fell in Class A and Class B, the 2 reasonably favorable for treatment. The table reflects the predominant use of radiation for cancer of the cervix in this vicinity.

Under the heading "combined treatment" are included those cases in which the patients received radon and X-ray treatment, or radon application, operation, and X-ray treatment. There are 32 in this group. Two cases received X-ray therapy only.

Of considerable interest is the variation in the total duration of the various forms of cervical cancers. Thus the average duration of the low grade epidermoid carcinomas (2.3 years) is twice that of the high grade and half again that of the cases of medium malignancy. It must be emphasized, of course, that these cases are all autopsies and, therefore, represent failures in treatment.

Evidence of the close correlation between the histological grade of the tumor and the distribution of metastases is further strengthened by the present study (Table II). One hundred and two of these 132 cases were pre-

TABLE III.—DEGREE OF MALIGNANCY AND NUMBER OF SITES OF METASTASES

Grade	Cases	Number of sites of metastasis
Epidermoid I.	25	19
Epidermoid II.	66	124
Epidermoid III.	21	68
Grade not stated.	4	0
Adeno-acanthoma.	5	10
Adenocarcinoma.	11	22

TABLE IV.—SITES OF METASTASES

Type		Regional nodes	Distant nodes	Adrenal	Bladder	Bone	Diaphragm	Gall bladder	Heart	Kidney	Intestine	Liver	Lung	Ovary	Pancreas	Peritoneum	Pleura	Skin	Spleen	Stomach	Thyroid
Epidermoid I	Before treatment	7	4									1									
	After treatment	3	3																		
Epidermoid II	Before treatment	24	17	1		1	2					4	4	1	1	2	1	1			
	After treatment	22	14	2		2				2	2	11	4		1	3			2		
Epidermoid III	Before treatment	12	12	2		2			1			8	5			1			1	1	
	After treatment	5	5						1	1	1	1	4			2	1		1		1
Adeno acanthoma	Before treatment	2	1									1	1	1							
	After treatment	3	1																		
Adenocarcinoma	Before treatment	3	2																		
	After treatment	3	4		1			1				2	2			3	1				
Total	Before treatment	48	36	3		3	2		1			14	10	2	1	3	1	1	1	1	
	After treatment	36	27	2	1	2		1	1	3	3	14	10		1	8	2		3		1

viously reported (2) with particular attention to the relation of grading to power of metastasis.

These consistent results are due in part to the fact that the estimation of the grade of malignancy in an autopsy is not restricted to a single small biopsy but an adequate amount of tissue is available for examination. In this way, a far more accurate determination of the grade is possible. Where there is marked variation in the histological appearance of a given tumor the less differentiated two-fifths of the portion studied has been used to determine the grade.

Too much stress can not be laid on the point that histological grading is of but little value in estimating individual prognosis. Here such factors as the extent of the local lesion, the presence of metastases, the age of the patient, the type of treatment utilized, must be given due weight. However, histological grading is of great value in determining the radiosensitivity of the tumor and in determining whether or not the tumor is likely to metastasize.

In this connection it might be well to emphasize that there is much confusion between radiosensitivity and what we might term radio-curability. In general the more rapidly growing, more anaplastic, more malignant tumors are sensitive to radiation and not infrequently the local growth is destroyed by the treatment. However, by virtue of their tendency to wide and early metastasis and deep local infiltration, in the long run these highly malignant tumors very frequently prove as unsatisfactory when treated by radium as by any other means. The difficulty, however, lies not in the failure of radiation to affect these radiosensitive tumors but rather in the failure of the field of effective radiation to include all of the malignant cells.

In the present paper we are chiefly concerned with the distribution of metastases. This distribution is summarized in Table II, and the close relationship between power of metastasis and histological grade of the tumor is brought out with extraordinary clarity. The percentage of variation in involvement of regional and distant lymph nodes and other organs by the different grades of tumors is shown in the figure, which presents graphically a portion of the material in Table II.

There is also close parallelism between the degree of malignancy and the total number of sites[1] of metastasis of the tumors of a given grade. This is brought out in Table III.

Thus the highly malignant epidermoid carcinomata average over three different sites of metastasis apiece, whereas those of low malignancy average less than one apiece.

In grade III epidermoid carcinoma such unusual sites as the heart, spleen, kidney, and thyroid have shown metastatic involvement.

Metastasis to bone is unusual in cervical cancers, but in this series it occurred five times, twice in grade III tumors and three times in grade II. The metastases were all of the osteoclastic type.

[1] A given group of nodes, as the sacral, is considered as a single site even though several nodes may be involved.

Table IV gives the detailed sites of metastases of the various types of cancers, together with an attempt to differentiate those metastases present before and those after treatment.

By careful study of the clinical record combined with study of the pathological processes themselves, I have attempted roughly to estimate the time at which various metastases appear. Eighty per cent of those occurring after treatment appeared within 1 year. Of course, the length of life after treatment in most cases was short.

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THE FATE OF THE SIDETRACKED LOOP OF ILEUM FOLLOWING LATERAL ANASTOMOSIS FOR COMPLETE, BENIGN OBSTRUCTION

A Clinical Experimental Study[1]

C. E. HOLM, M.D., M.M.Sc., Allentown, Pennsylvania

FOLLOWING a simple lateral ileo-ileostomy or ileocolostomy for complete benign obstruction of the terminal ileum, the loop of ileum between the anastomosis and the obstruction may give rise to serious trouble, as evidenced by the following case reports reviewed at the suggestion of Dr. W. L. Estes, Jr., made to me while serving as resident surgeon at St. Luke's Hospital, Bethlehem, Pennsylvania.

Case 1. F. B., male, aged 12 years, was admitted to St. Luke's Hospital, June 11, 1929. Three days before admission the patient was seized with acute appendicitis, and at operation—1 hour after admission—a gangrenous, perforated appendix was found within a large abscess walled off by intestinal coils. Appendectomy was done and the abdominal cavity drained. Convalescence was prolonged because of wound infection, but was otherwise uneventful. At a follow-up examination on October 17, 1929, the patient was in excellent health. He remained free from abdominal symptoms until April 5, 1930, when intestinal obstruction occurred. Following his readmission to the hospital on April 7, repeated enemata failed to give relief and an operation was performed 3 hours later. The terminal 3 feet of ileum was adherent to itself, to the cæcum, and to the anterior abdominal wall. Adhesions were divided to release a 3 inch loop of strangulated but viable ileum. Inasmuch as adhesions threatened future strangulation, a lateral anastomosis was established between the transverse colon and the ileum at a point 3 feet proximal to the cæcum.

Throughout the convalescent period the patient had a good appetite and his general condition was excellent. A mild, painless diarrhœa, with considerable borborygmus and moderate distention of the lower abdomen developed 1 week before his discharge on April 22, continued in a mild form until May 4 when the diarrhœa became severe, and vomiting occurred 2 days later. These symptoms became progressively worse and at admission to the hospital on May 9 the patient was found to be undernourished, dehydrated, drowsy, and very toxic. The abdomen was moderately distended and generally tender, but there was neither rigidity nor palpable mass. At operation the following morning the terminal 3 feet of ileum sidetracked on April 7 was found elongated to 7 feet, greatly dilated, acutely inflamed and ulcerated, with the distal 1 foot completely obstructed in a mass of adhesions. The meso-ileum contained many lymph nodes varying in size from a pea to a walnut. The colon was collapsed proximal and distal to the anastomosis. The sidetracked loop was resected, from the anastomosis to the cæcum. During the manipulations of resection, several ulcerations of the loop perforated. The abdominal cavity was drained. A serious wound infection and a continuance of the pre-operative debility prolonged the convalescence. A mild diarrhœa persisted throughout the patient's stay in the hospital and continued for several months after his discharge. Recuperation was slow for several months following his return home, but at the last follow up examination in May, 1931, he had gained 25 pounds in weight and his general health was excellent.

Case 2. S. D., a boy of 16 years, was admitted to the hospital November 18, 1928, with symptoms and signs of acute intestinal obstruction of 2 days' duration. At operation several loops of terminal ileum were found matted together and adherent to the lateral wall of the pelvis, around a gangrenous Meckel's diverticulum. The ileum was completely obstructed at a point near the cæcum. The involved loops of ileum were resected, following which a lateral anastomosis was performed between the ascending colon, and the ileum 8 inches proximal to the resection. The 8 inch limb of ileum distal to the anastomosis was placed over a large defect in the posterior parietal peritoneum. The abdomen was closed with drainage. Ten days after operation the patient became slightly distended, and began having mild attacks of visible peristalsis which recurred during the remainder of his stay in the hospital. His general condition was good. After going home on December 7, 1928, visible peristalsis recurred with increasing frequency and was associated with marked borborygmus and pain. He had from two to six loose bowel movements daily. His symptoms becoming progressively worse, he was readmitted on January 26, 1929, and was operated upon 2 days later. The 8 inches of blind ileum distal to the anastomosis performed the previous November had become greatly elongated and distended, and it filled the lower half of the abdominal cavity. It was coiled upon itself, with dense adhesions to the cæcum and pelvic wall. The blind end of the ileum was partially freed from adhesions when the patient's general condition became too serious to permit resection, and the operation was hastily terminated by performing a lateral ileo-ileostomy between a point near the end of the blind limb and an area immediately distal to the former ileocolostomy. Recovery was prompt and the patient was discharged on February 9.

[1]From the Graduate School of Medicine and the Laboratory of Research Surgery, University of Pennsylvania, Philadelphia, and St. Luke's Hospital, Bethlehem, Pennsylvania.

Fig. 1.

Fig. 2.

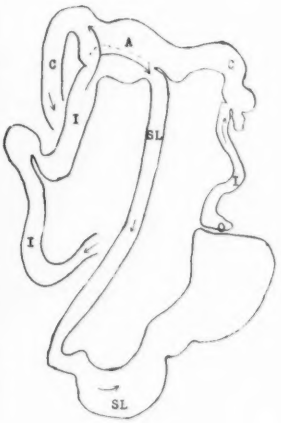

Fig. 3.

Fig. 1. Roentgenographic evidence of a dilated intestinal loop noted 7 weeks following lateral anastomosis between ileum and colon.

Fig. 2. Photograph showing dilatation and elongation of sidetracked ileal loop following the operation of lateral ileocolostomy for the relief of complete obstruction of terminal ileum.

Fig. 3. Diagram explaining photograph in Figure 2. *A*, Anastomosis; *C*, colon; *I*, ileum; *O*, obstruction; *SL*, sidetracked loop.

At a follow-up examination on September 21, 1929, the patient was much underweight, due to a severe diarrhœa of 4 months' duration. There had been occasional attacks of distention, borborygmus, and painful peristalsis. He was placed on a strict diet and on January 2, 1930, was greatly improved, although abdominal distention and a mild diarrhœa had persisted. His appetite had been good throughout.

The patient was readmitted on January 7, 1930, during an aggravation of the abdominal symptoms, and he was operated on 3 days later. The lower two-thirds of the abdominal cavity was filled with the further elongated and dilated, blind loop of terminal ileum. Proximal to the ileocolostomy, the ileum seemed normal. The blind loop of ileum was freed of adhesions and resected at a point close to the ileocolostomy, and the sigmoid was sutured over the denuded areas. The patient was discharged on January 28 greatly improved, although he had a mild diarrhœa. The diarrhœa persisted for several weeks after his return home. At the final follow-up examination on May 8, 1931, the patient was in excellent health.

A search of the literature on intestinal obstruction disclosed only an occasional clinical reference to complications occurring in the sidetracked loop of ileum following a lateral anastomosis for complete obstruction, which necessitated secondary operation and resection; and failed to reveal reports of experimental work on this problem. In order to determine the fate of the sidetracked loop after lateral ileo-ileostomy or ileocolostomy for an induced, complete, and permanent obstruction of the terminal ileum, 7 dogs were operated upon. After operation all of the dogs were fed a liquid diet for 4 days, a soft diet for 3 to 4 weeks, and thereafter a general diet. Fluoroscopic studies of the intestinal tract were made on 5 dogs several weeks after operation to ascertain, without sacrificing the animals, if dilatation of the sidetracked loops had occurred.

Fig. 4.

Fig. 5.

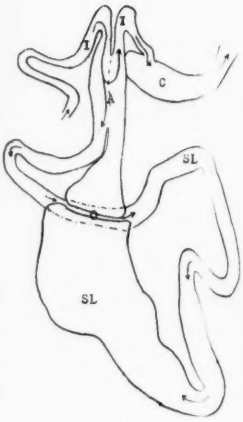

Fig. 6.

Fig. 4. Roentgenogram showing dilated loop of intestine.

Fig. 5. An elongated and dilated loop of sidetracked ileum after lateral ileo-ileostomy for complete obstruction.

Fig. 6. A drawing illustrating the condition which is shown in the photograph of the intestines, Figure 5. *A*, Anastomosis; *C*, colon; *I*, ileum; *O*, obstruction; *SL*, sidetracked loop.

Three typical protocols are given below, followed by abstracts of four others.

Dog 575. An obstruction was created in the ileum 5 inches proximal to the cæcum by severing the bowel transversely and inverting both ends. The closed ends were approximated by sutures in order to maintain the general relations of the ileum. This was followed immediately by a lateral anastomosis between the ileum 14 inches proximal to the obstruction and the colon 5 inches distal to the ileocæcal juncture.

The dog made an uneventful postoperative recovery and for 4 weeks was well and active, with good appetite and normal bowel movements. At the end of this time he became listless, lost weight, developed slight distention, and a mild diarrhœa occurred which became progressively worse. At the end of 7 weeks when fluoroscopic studies were made, borborygmus was evident and peristalsis was extremely hyperactive. A large dilated loop of bowel was disclosed and a roentgenogram was taken (Fig. 1). Severe diarrhœa and weight loss continued, but other symptoms improved. The dog was sacrificed 94 days after operation and an autopsy was performed immediately.

The abdomen was free from infection, and the anastomosis was well healed with a stoma 1¼ inches in length. The sidetracked loop of ileum had elongated from 14 inches to 22 inches and the terminal 8 inches was dilated from three to four times the normal caliber, with generalized thinning of the walls. The meso-ileum contained numerous lymph nodes enlarged up to 1½ inches in diameter. The dilated loop and adjacent bowel were placed on the abdominal wall of the dog and photographed (Figs. 2, 3); then removed and placed in formalin solution.

When the specimen was opened a small mass of hair and indigestible matter was found in the dilated loop, and the walls of the terminal 4 inches were very thin with many superficial ulcerations. The adjacent proximal 2 inches seemed normal, but the remainder of the sidetracked loop contained several areas with thin walls and ulceration of the mucosa. There were several ulcerated thin walled areas in the ileum proximal to the anastomosis, and also in the colon proximal and distal to the anastomosis. The remainder of the specimen seemed normal.

Sections from the right lobe of the liver and from the right kidney were macroscopically normal.

Microscopic sections of the dilated and thinwalled portion of the loop showed some areas of mucosa

Fig. 7.

Fig. 8.

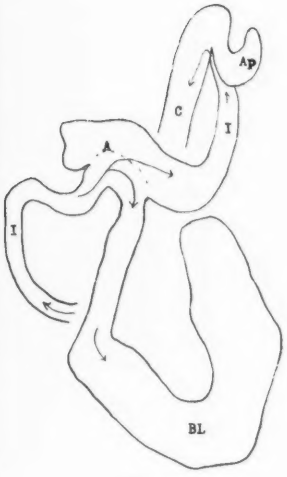

Fig. 9.

Fig. 7. A dilated loop of intestine revealed by the X-ray.
Fig. 8. Photograph showing an elongation and dilatation of blind limb of ileum distal to lateral ileo-ileostomy.

Fig. 9. A graphic explanation of Figure 8. *A*, Anastomosis; *Ap*, appendix; *C*, colon; *I*, condition in ileum; *BL*, blind limb.

replaced by an ulcerative process made up mainly of plasma cells and fibroblasts, and other areas of small round cell infiltration extending well into the muscular layer. Sections from a grossly normal portion of the sidetracked loop disclosed hypertrophy of the muscular layer, and marked swelling of the mucosa with diffuse small round cell infiltration, lymphocytes and plasma cells predominating. Proximal to the anastomosis, the mucosa exhibited a mild degeneration and small round cell infiltration, while the muscular coat was extremely thin with considerable round cell infiltration, polymorphonuclear leucocytes in the minority. The macroscopically normal colon exhibited a complete loss of the staining quality of nuclei of mucosal cells. The liver showed widespread cloudy swelling and parenchymatous degeneration, most pronounced around the central portion of the lobules. The kidney exhibited considerable vascular injection, and severe glomerular and tubular degeneration, with areas of small round cell interstitial infiltration.

Dog 499. An ileal obstruction was produced 6 inches from the cæcum and a lateral ileo-ileostomy was established between points of the ileum 16 inches proximal, 3 inches distal to the obstruction.

The immediate postoperative recovery was unimportant and the dog remained well and active for 5 weeks, when diarrhœa developed and became increasingly more severe, with slight distention and borborygmus. He lost weight, but remained active and bright. Fluoroscopic examinations 6 and 7 weeks after operation demonstrated hyperactive peristalsis and a dilated loop of intestine. Roentgenogram is shown in Figure 4. Symptoms did not change during the following 7 weeks, except for lassitude and continued weight loss. The dog was sacrificed 14 weeks and 5 days after operation.

At autopsy, the anastomosis was firmly healed around a stoma about 2 inches in length. The sidetracked loop of ileum had elongated from 16 inches to 28 inches and the terminal 8 to 9 inches had dilated to about four times the normal diameter. The walls were very thin in many areas, although the terminal 4 or 5 inches seemed to be hypertrophied. There was slight dilatation of the ileum for 1 inch beyond the obstruction. The colon, and the ileum proximal to the anastomosis seemed normal. There were many large lymph nodes in the meso-ileum. The intestines were photographed (Figs. 5 and 6), and then placed in formalin solution. Sections of normal appearing tissue were removed from the right lobe of the liver and the right kidney.

When the specimen was opened the terminal 5 inches of the dilated loop were found definitely hypertrophied with scattered ulcerations.

The 8 inches proximal to this were thin walled with many deep ulcerations. There were scattered ulcers in the remainder of the loop and distal to the obstruction. The colon and the remainder of the ileum seemed normal.

In a microscopical section taken from the hypertrophied portion of the dilated loop, the muscle layer was greatly thickened with a degeneration of muscle fibers, many of which were displaced by inflammatory tissue. The mucosa was markedly degenerated, necrosed, and infiltrated with inflammatory cells. The ileum 10 inches proximal to the anastomosis manifested slight degeneration of the mucosa and muscular layers. The liver exhibited widespread and intense fatty infiltration, with pigmentation of the liver cells, most pronounced around the central veins. There was vascular congestion, and some of the central veins had thickened walls, while others were occluded with blood cells undergoing organization. The kidney showed advanced tubular, and moderate glomerular degeneration.

Dog 657. The operative procedures on this dog were designed to simulate those in clinical Case 2. The ileum was severed transversely 6 inches from the ileocæcal juncture and its ends were turned in. A lateral ileo-ileostomy was performed allowing the proximal end of the ileum to extend 8 inches beyond the anastomosis.

The immediate postoperative recovery was uneventful. Diarrhœa developed in 3 weeks and became increasingly more severe. There was listlessness, slight distention, and considerable weight loss at the end of 6 weeks. The fluoroscope demonstrated a dilated loop 6 weeks after operation. A roentgenogram was made (Fig. 7). The condition of the dog remained unchanged during the next 4 weeks, and he was sacrificed 10 weeks and 3 days after operation. The appetite was well maintained throughout.

At autopsy, performed very soon after death, there was no evidence of peritonitis, the anastomosis was well healed, and the stoma was 1½ inches in diameter. The blind limb of ileum had elongated from 8 to 16 inches and the terminal 8 inches had dilated to three times the normal caliber, with the walls generally thin (Figs. 8 and 9). The lymph nodes in the meso-ileum were greatly enlarged. The section was removed and placed in formalin solution. Seemingly normal tissue was removed from the right lobe of the liver and from the right kidney.

When the specimen had been opened the terminal 4 inches of the dilated limb were found hypertrophied with many small ulcerations. The walls in the remainder of the loop were thin and ulcerated. There were scattered ulcerations in the ileum proximal to the anastomosis, between the anastomosis and the cæcum, and in the colon.

Microscopically, a section from a thin portion of the dilated limb manifested marked degeneration and necrosis of the mucosa, extending to the muscle layer. A section from a thick portion of the limb displayed degeneration and necrosis of the surface of the mucosa. Sections from normal appearing colon showed small round cell infiltration and slight degeneration of the mucosa. The liver and the kidney exhibited the same type of widespread degenerative changes seen in the other dogs.

Dog 487. Obstruction was produced and an ileocolostomy was established as in dog 575. The immediate postoperative course was similar to those described in the protocols of the other dogs. Death occurred 6½ weeks after operation from general peritonitis, due to a perforation in the obstructed loop. Gross and microscopical findings were much the same as those described in the three protocols. The terminal 3 inches of the sidetracked loop were hypertrophied.

Dog 651. Operative procedures were the same as in dogs 575 and 487. Postoperative symptoms and physical findings were almost identical to those previously described. A dilated loop of intestine was observed fluoroscopically after a barium meal at the end of 5 weeks. The dog was sacrificed during the ninth week. Macroscopically and microscopically the findings were similar to those in the other dogs.

Dog 713. Obstruction and ileo-ileostomy was done as in dog 499. The postoperative course was practically the same as that of all the other dogs until death occurred 6 weeks after operation from general peritonitis resulting from a perforation in the obstructed loop. Gross and microscopic findings were similar to those found in the other dogs. The terminal 1½ inches of the obstructed loop was hypertrophied.

Dog 492. A lateral ileo-ileostomy was performed as in dog 657, leaving a blind limb 6 inches long. The postoperative course was about the same as that of the other animals. Fluoroscopic evidence of a dilated intestinal limb was seen at the end of 7 weeks. It was necessary to sacrifice the animal 13 weeks after operation because of extreme emaciation and debility. The terminal 5 inches of the enlarged blind limb were hypertrophied. Macroscopic and microscopic findings were similar to those observed in the other animals, but in all instances the degenerative changes were more advanced.

SUMMARY

In two clinical cases of complete obstruction in the terminal ileum resulting from adhesions, various types of lateral anastomoses were done without removal of the ileum between the anastomosis and the obstruction. Following the anastomoses the patient developed diarrhœa, borborygmus, abdominal distention, marked weight loss and debility, without impairment of appetite. In each

patient complete recovery followed resection of the sidetracked loop, which was greatly elongated, markedly dilated, and ulcerated.

An intestinal obstruction was produced in the terminal ileum in 7 dogs, following which various types of lateral anastomoses were done, allowing the sidetracked loops to remain. After operation all of the dogs developed diarrhœa, borborygmus, distention, weight loss, and debility, but maintained a good appetite. Two dogs died from general peritonitis resulting from perforation of the sidetracked loop. Five dogs were sacrificed. In all 7 dogs the sidetracked loop was found markedly elongated, greatly dilated, and ulcerated. Microscopic sections showed areas of deep and superficial ulceration in the dilated loops; superficial mucosal ulceration of the ileum and colon remote from the sidetracked loops; and widespread, advanced degenerative changes in liver and kidney.

CLINICAL APPLICATION OF EXPERIMENT

The terminal ileum was selected for study in the experimental work because it is a common site for obstruction from adhesions as evidenced by the two clinical cases.

Photographs of roentgenograms, and dilated sidetracked loops displayed on the abdomens of the dogs have been omitted in the abstracts of the four protocols because they were practically identical to those presented.

The more advanced liver and kidney changes in two dogs might have been due, in part, to the general peritonitis.

The superficial necrosis of the mucosa in the intestines remote from the sidetracked loop, indicated a general enterocolitis as the cause of the severe diarrhœa in all of the animals. It is assumed that a similar condition existed in the two clinical cases reported and was responsible for the diarrhœa which persisted throughout their illnesses, and for several months after resection of the sidetracked loops.

The type of degenerative changes observed in the liver and kidney sections from the dogs probably were present in the 2 patients and might have been a factor in the toxicity which they displayed and the period of slow recuperation which followed resection.

The postoperative signs and symptoms occurring in all of the dogs were similar to those observed in the two patients prior to resection of the sidetracked loop.

Fluoroscopic and X-ray examination aid diagnosis in detecting elongation and dilatation of the sidetracked loop of ileum in patients who exhibit the symptoms and signs of the two clinical cases.

Surgeons generally recognize that it is not advisable to permit a blind limb to extend beyond a side-to-side anastomosis. In any lateral anastomosis for permanent, complete obstruction the sidetracked loop corresponds to a blind limb extending beyond the anastomosis.

CONCLUSIONS

1. The sidetracked ileal loop of a lateral ileo-ileostomy or ileocolostomy for complete, benign obstruction of the terminal ileum is likely to become greatly elongated, dilated, and ulcerated. An enterocolitis with mucosal degeneration, and degenerative lesions of the liver and kidneys will probably develop.

2. Whenever possible, the sidetracked ileum should be resected at the time the lateral anastomosis is done.

3. If resection is inadvisable because of the condition of the patient, the lateral anastomosis should be done as near the obstruction as possible, and should be regarded only as a first stage operation, to be followed by a resection of the sidetracked loop of ileum at a more favorable time.

4. As an alternative procedure it is suggested that the ileum might be divided as close to the obstructive lesion as possible and be followed by an end-to-side anastomosis, which eliminates a blind end.

LIGHT AND TAR CANCER

An Experimental Study, with a Critical Review of the Literature on Light as a Carcinogenic Factor

M. G. SEELIG, M.D., F.A.C.S., and ZOLA K. COOPER, Ph.D., St. Louis, Missouri
From the Research Laboratory of The Barnard Free Skin and Cancer Hospital

Part I. Experimental Study

DESPITE the fact that the rôle of light in the genesis and development of cancer is of interest both experimentally and clinically, very little clear-cut experimental work has been done upon this subject. Part II of this paper, a critical review of the literature on light as a carcinogenic factor, emphasizes the necessity for well controlled experimental data. With the object of collecting such data, we attempted to determine the carcinogenic effect of tar applied to mice, kept in an environment from which light was totally excluded.

Material and methods. In one corner of our animal room, a light proof chamber, 18 by 15 by 12 feet, was built, two sides of which were made up of the south and east walls of the animal room, and the other two sides of 0.5 inch fiber board (Masonite) that extended from floor to ceiling. There were three windows in the original wall space. Instead of walling in these windows, light traps were built about them so as to permit the entrance of air and to exclude light. The entrance to the room was through a light proof maze, built of fiber board. All joints and crevices in the fiber board walls were made light proof by caulking. A 14 inch galvanized iron flue pipe, painted black on the inside and furnished with light blocking baffles, entered through a light tight opening and led to an exhaust fan within the dark room. In this manner a constant stream of fresh air was kept moving from the windows out through the exhaust duct. In the room were two steam radiators, by means of which the temperature could be regulated. The room was furnished with racks for mice cages, a work bench provided with a ruby light, and storage places for animal food,[1] tar, and various accessories. This room assured total darkness and an environment that was otherwise comparable to that in which mice live out their natural lives in the ordinary well constructed animal room. After the room was built, a set of highly sensitive photographic plates were exposed in it for 48 hours. When developed, these plates showed no evidence of being light struck.

The tar used in these experiments was distilled so that only the fraction coming off at 370 to 440 degrees C. was collected. This distillation[2] was so executed that this tar fraction (370 to 440 degrees C.) was not exposed to light during the process. The tar was then kept stored in the dark room, in light proof receptacles.

Three sets of mice were segregated for the experiment: (1) 125 male mice, approximately 3 months old, were set apart for tarring in the dark; (2) a similar group of 125 were set apart for tarring in the light; and (3) a similar group of 50 were kept as controls in the dark room. This last group was not tarred and was used merely as a check on living conditions in the dark. The experiment was not begun until the mice had been kept in the dark for 3 weeks.

After the elapse of this preliminary period, the group of 125 mice kept in the dark were tarred, as were the similar group kept in the light. After preliminary depilation with sodium sulphide, tar was applied between the scapulæ, once or twice a week until the animals died. A complete autopsy was performed on every mouse. All skin lesions and all suspicious visceral nodules were removed and examined in microscopic sections.

It was not until the experiment had run almost 4 months that we fully realized the advisability of using genetically bred mice. The comments of Little have much force, even

[1] As an added precaution, the animal food (chiefly cracked corn) was kept in the dark room. The green stuff and bread and milk, which were necessary in the diet of the mice, could not be kept entirely unexposed to light.

[2] We are indebted to Messrs. D. Wilson and J. Kohlberg, of the Laclede Gas Light Company of St. Louis, for their courteous and enthusiastic co-operation in furnishing us our tar distillate.

though one may not be willing to subscribe unqualifiedly to his statement that "it is, today, as careless to use unknown genetic material in experimental pathology, as it is for a chemist to attempt to analyze substances, using unknown, rather than known, reagents." After much soul searching, we decided to present our data, such as it was, rather than to start the long drawn out procedure of raising 300 genetically bred mice, and starting the experiment anew. We were emboldened in this position by the fact, as emphasized by Roffo, that in tar cancer, the receptivity or susceptibility varies, not only in animals of different species and in animals of near relationship, but even among animals of the same family. Moreover, susceptibility varies in different anatomical sites of the same animal, and possibly even in cells of the same anatomical site. Twort and Twort emphasize, in particular, the impossibility of establishing a standard value of the unit of carcinogenicity. Reinhard and Candee found that strains of mice with either a high or low incidence of spontaneous cancer responded similarly to tarring, except that the latent period, in the low incidence strain, was 14 weeks longer than in the high. Parodi found also that individual susceptibility varied, even in a strain of genetically bred mice. These several observations, in addition to Roffo's testimony, strengthened us in our determination to run the experiment through with ordinary laboratory mice.

GROUP I. 125 MICE, TARRED 23 TIMES DURING A PERIOD OF RESIDENCE IN TOTAL DARKNESS OF 27 WEEKS

After living for 3 weeks in the dark, the mice of this group were tarred with the high fraction tar distillate, already mentioned. The tar was applied to the interscapular region at the root of the neck, over an area about 1.5 centimeters in diameter. At first these applications were made every third day, but our tar proved to be so highly toxic that we varied the time interval between paintings to meet the problem of high death rate. The last animal in the group died 24 weeks after the first application of tar, and during this period tar was applied 23 times. During the last 4 weeks of the experiment, no application of tar was made. In the early part of the experiment, crust was removed as it formed at the site of application of the tar, but since this seemed to favor toxic absorption of the tar, we, later, let the crust drop off spontaneously.

When an animal died, a complete autopsy was performed, the tarred area was excised and paraffin sections of it prepared. From the outset, we determined to call only those growths carcinomata in which we could demonstrate that the neoplastic epithelium infiltrated the subcutaneous muscle layers. It scarcely seems advisable, in this report, to go into the lengthy and intricate chapter of the essential histological criteria of tar cancer. Those who are interested will find the subject discussed by Woglom, and by Seelig and Cooper. Here it suffices to say that intramuscular infiltration seemed to us to be, of all others, the most satisfactory and reliable basis for the diagnosis of cancer. We avoid the use of the terms epithelioma and cancroid, and, although in several of our mice (in the group kept in the dark, and likewise in the group kept in the light), the cell morphology, growth, tinctorial reaction, and mitotic activity of the lesions, pointed indubitably to the diagnosis of cancer, we did not record the tumor as such unless it infiltrated out of bounds, into muscle tissue.

In Group I, thickening and keratosis of the skin was noticeable, macroscopically, 2 weeks after the first application of tar. At about 8 weeks after the first painting, papillomata began to appear. Some of these growths, which macroscopically appeared to be papillomata, proved microscopically to be more on the order of keratotic warts. After 4 weeks of tarring, 27 mice had died, a mortality rate of slightly over 20 per cent. Part of this high mortality rate (which was paralleled by the control group, tarred in the light) was due to toxic effects of the tar, and part of it to an epidemic of diarrhœa, which invaded the entire colony of laboratory at this time. Later, our animals suffered from what seemed to be an epidemic form of pneumonia. However, the death rate among the animals used in this experiment was not high enough to invalidate our final results.

Beginning with the eighth week, papillomata were abundant, and from then on, these papillomata either showed a tendency to develop induration about the base, or to ulcerate. Some of them dropped off, to be replaced by new papillomata.

By the end of the eighth week, approximately 50 per cent of the animals had died; by the end of the twelfth week, 70 per cent; by the end of the twentieth week, 90 per cent. There were now 8 surviving animals which succumbed one by one, the last one dying 24 weeks after the beginning of tarring. An analysis of this mortality rate discloses that if we assume dogmatically that we might expect carcinogenesis to develop about the tenth week, then at this time 47 of our original group of 125 mice remained alive. Of these 47 mice that remained, 11 mice developed carcinomata, conforming to the histological criteria already described. The tumors were all of the squamous cell type, and all of them presented histological evidences of very active growth (mitoses, markedly anaplastic cells,—both with regard to size and shape of the cells, and variations in tinctorial reaction,—and very little evidence of keratinization or pearl formation).

Visceral metastases were found in only 2 of the 125 mice in Group I. These 2 animals showed squamous cell carcinomata of the lungs. In one mouse, a regional lymph node of the root of the neck showed a metastatic squamous cell carcinoma. (In the case of the lymph node, it was quite apparent that we were dealing with a metastatic focus; but we are unwilling to dogmatize regarding the carcinomatous foci in the lung, for we know of no reliable method of differentiating primary or spontaneous carcinomata of the lungs from secondary or metastatic foci).

The 11 mice that developed carcinomata died 110, 116, 125, 136, 139, 146, 147, 150, 153, 155, and 157 days, respectively, after the beginning of tarring. In view of the fact that our plan was to examine tissues only after the animals had lived out their lives, and that we were unwilling to add the element of trauma, incident to performing a biopsy, we cannot furnish data regarding the earliest time at which the cancers were demonstrable. The most that we can say is that 11 out of a series of 125 mice developed cancer (approximately 9 per cent), and that the average duration of life of these mice was 140 days after the beginning of tarring.

In Group I, 2 mice developed growths that showed all the other characteristics of malignancy, but that did not infiltrate muscle. We did not classify these tumors as malignant.

GROUP II. 125 MICE, TARRED 27 TIMES DURING A PERIOD OF RESIDENCE IN THE LIGHT OF 32 WEEKS

In this control group, as in Group I, we found that owing to the toxicity of our tar, we could not make the applications on fixed dates, or at predetermined intervals. The last animal in this group died 32 weeks after tarring was begun, and during this period, tar was applied 27 times. It will be noted, therefore, that the length of the experiment was 5 weeks greater than that of Group I, and that 4 more applications of tar were made. It scarcely seems warrantable from these facts to draw any specific conclusions regarding the influence of light on the general hygiene and duration of life of the animals, or on the toxicity of tar.

In this group, just as in Group I, each animal was permitted to live out its life, pathological examinations being made in every instance after death. Macroscopically no essential differences from Group I were apparent in this group, with regard to crusting, thickening of the skin, keratosis, or development of papillomata. At the end of the sixteenth week, the mortality rate was 85 per cent, as contrasted with 84 per cent in Group I; by the end of the twentieth week, the mortality was 90 per cent as contrasted with 88 per cent in Group I. The last animal died 228 days after the tarring was begun. A particularly interesting phase of the comparative mortality rate in the two groups, is that the early mortality was much greater among the animals of Group I. For example, at the end of 4 weeks, the mortality rate in Group I was 23 per cent, whereas in Group II, it was 9 per cent (see Table I).

The significance of this difference in mortality rate lies in the fact that a larger number

of mice in Group II received applications of tar over a longer period of time than in Group I. Despite this, in Group II, only 5 carcinomata developed, as contrasted with 11 that developed in Group I. In all of the animals the tumors were of the same histological type as those in Group I, and in one animal there developed a squamous cell carcinoma of the lung, which we considered metastatic. In this group the first animal in which carcinoma was found, died 161 days after painting began, the other 4 animals dying, respectively, 172, 194, 198, and 221 days after the beginning of painting. Compared with Group I, these figures would seem to indicate a delayed effect; but since we had no way of determining exactly when the cancers developed, we do not feel warranted in stressing the time element.

In this group, there were 3 mice with tumors that showed all the other characteristics of malignancy but that did not infiltrate muscle. We did not classify these tumors as carcinomata.

TABLE I.—MORTALITY RATES

	Group I. Tarred in the dark	Group II. Tarred in the light	Group III Not tarred in the dark
Number of mice	125	125	50
Duration of experiment	24 (weeks)	32 (weeks)	22 (weeks)
Number of tarrings	23	27	0
Number of carcinomata	11	5	0
Per cent of mice developing carcinomata	8.8	4	0
Number of metastases	2	1	0
Mortality per cent			
4th week	23.2	9.6	0.0
8th week	49.6	48.8	0.0
12th week	68.8	77.6	30.0
16th week	84.8	85.6	58.0
20th week	93.6	92.8	58.0
24th week	100.0	96.0	*
28th week		98.4	
32nd week		100.0	

*Experiment discontinued after 22nd week—42 per cent of animals still living and well.

GROUP III. 50 MICE, UNTARRED, KEPT IN THE DARK FOR 22 WEEKS

This group was used merely to check the effect of living conditions in the dark room. An unusually high mortality rate might have indicated that darkness alone exercises a marked constitutional effect on the animals. However, when the last of the tarred animals died, in the dark, 21 of the original 50 of the untarred animals of Group III were still living. This represents a mortality rate of 58 per cent, which is not abnormally high for a group of 50 mice, over a period of 22 weeks, if we bear in mind the two epidemics already mentioned. It would seem, therefore, that complete darkness in itself does not influence the general condition, nor the mortality rate of the mice to a degree that in any way affects the experiment.

CONCLUSIONS

1. The absence of light did not cause any physical compromise in a group of mice subjected to total darkness over a period of approximately 5 months.

2. White light is not a necessary factor in the development of tar cancer in mice, because in total darkness, in the group of mice used in these experiments, a larger number of tar cancers developed than developed in a similar group of mice that were tarred and kept in the light.

3. The comparatively larger number of carcinomata occurring in the mice kept in the dark is too small to warrant the conclusion that the absence of light in itself favors the development of tar cancer in mice.

4. These experiments do not eliminate the possibility that light may be a secondary factor in the genesis of experimental cancer. They furthermore do not warrant dogmatic and direct deductions applicable to human cancer.

PART II. A CRITICAL REVIEW OF THE LITERATURE ON LIGHT AS A CARCINOGENIC FACTOR

Ten years before the beginning of the present century, the Hamburg dermatologist, Unna, made elaborate histological studies of the influence of light on the development of cancer. These studies were made in relation to the development of cancer in Xeroderma pigmentosum, and in "sailors' skin" (a disease described originally by Unna). Unna

announced that light was the noxious agency in the production of these two special forms of cancer, and that the histological changes to be noted in the precancerous skin lesions (capillary hyperæmia, venous ectasis, hyperkeratosis, sclerosis of the skin surface, and pigmentation) indicated endeavors on the part of the skin to neutralize the injurious influence of light. The pigmentation blocks all light and the hyperæmia protects the deeper structures by cutting out the highly actinic blue rays (as does the photographer's ruby light). The hyperkeratosis, sclerosis, and capillary atrophy of the papillary bodies operate not by arresting the light, but rather by diminishing its influence on cutaneous tissues that are "less sensitive, drier, harder, more tendonous and callous."

Watkins-Pitchford, in 1909, attempted to develop an all embracing theory that "cancer, whether of special sections of community life, or of special parts of the body of the individual, is caused by an illumination in excess of that which can be dealt with by the protective agencies of habit, posture, coverings and external pigmentation, and in excess of that which may be controlled by the agencies of internal pigmentation and cell-memory-for-former-environment"; that "the generally increased liability of man as compared with the lower mammalia is chargeable against the comparative novelty of his attitude, and almost complete loss of his hairy coat"; that "the special liability of the white man, as compared with the black man, is due to the loss of pigmentation and to his changed environment"; and finally, that "these liabilities do not show themselves in the individual as vague, general and constitutional predisposition, but are strictly confined to those parts of the body in which irradiation becomes excessive."

Watkins-Pitchford characterizes his thirty page prize essay as purely "an induction from observation." It is all of this and nothing more. The author has assembled, however, a striking amount of comparative anatomical, physiological, pathological, and ethnological data in support of an hypothesis, which he leaves unproved. Hoffman suggests that the high incidence of cancer among seamen and fishermen may lend support to Watkins-Pitchford's hypothesis. This is possibly true; but a great deal of support would be necessary in order to furnish essential strength to an hypothesis that makes light *the* agency in the causation of cancer.

Paul states that the most important cutaneous lesions in Australia (viewed from the standpoint of prevalence and destructive effects) are rodent ulcer and "epithelioma." He believes that the most significant causative factors of these lesions are the actinic rays of light, and that the most significant inhibiting factor is the pigment deposit in the skin, particularly noted in the colored races occupying the tropical and subtropical countries. In these people, the effect of sunlight is minimal despite the fact that exposure to it is most severe and long continued.

Paul believes that melanin stands as a skin sentinel, protecting the underlying tissues from the baneful effects of sunlight. In the white races, this pigment is confined, for the most part, to the periphery of the cells of the basal layer of the epidermis, and the lowermost stratum of the prickle cell layer, while the pigment granules may also be found in the interepithelial spaces and in the fusiform connective tissue cells of the papillary body. Paul quotes Macleod as authority for the statement that, in the dark races, pigment is to be found as high up as the transitional layers of the epidermis, as well as in some of the connective tissue cells of the superficial portions of the corium.

Watkins-Pitchford and Paul are not the only authors who stress the possibility of making the actinic light rays responsible for skin cancer. Duhíg also thinks that they are the sole factors responsible for that disease, though he admits that the evidence on which his belief rests is indirect. Duhíg is pathologist to the Coast Hospitals Board, and to the Brisbane Hospital, in Queensland, Australia, where he gathered the data on which he bases the following statements:

> Cancer of the skin is four times more common in males than in females, and in those females affected, considerable periods of exposure to the strong sunlight of Queensland have been known to occur. Those males affected, almost invariably give a good

history of exposure. Also the disease is one preponderantly of life beyond the middle years; that is, the longer the exposure, the greater the incidence, while lack of exposure runs concurrent with the absence of the disease, even in advanced life.

The disease occurs practically exclusively on those parts of the body constantly exposed to sunlight. In 3 cases only of nearly 500 investigated, did cancer occur on habitually unexposed skin—once on the foot, probably as the result of trauma, once on the thigh for a similar reason, and once on the thoracic wall, for no discoverable reason. The disease occurs preponderantly on the face, ears, and neck, and on the back of the hands in only about 5 per cent of the cases. Cancer of the back of the neck is almost exclusively confined to males at present, though I would predict that as a result of the fashion of short hair, and the very silly one of berets and cloche, and similar brimless hats in summer, affected by women in this country in an effort to keep up with the overseas magazine life, cancer of that part of the body will be later just as common among women as now amongst men.

It is strange that no direct evidence of an experimental kind is available as to the effect of sunlight on the human skin, though some little work has been done on the effect of the ultraviolet and of the spectrum. I do not know that it is necessary to prove, experimentally, the bad effect of direct sunlight on the human skin; to me such work would only go to confirm my present opinion that *skin cancer is solely due to excessive exposure to sunlight.* It is commonly believed that only persons of ruddy complexions accompanied by russet or reddish hair are susceptible. After a long experience, I would say that probably, susceptibility is inversely proportional to abundance of skin pigment in a general way, but that a brunette complexion is not a safeguard. It is a very significant fact, however, that cancer of the skin does not occur in India, to any extent among the native races.

In an article on cancer in the negro, Hoffman furnishes a veritable storehouse of information on the subject of cancer in the dark skinned races of the world. The data presented by Hoffman is so highly statistical and his reasoning so closely knit that an injustice would be done him by an attempt to abridge his article within short compass. He does, however, make categorical statements to the effect that (1) cancer mortality of the American negro tends more and more to approach that of the white population, as the result of a persistent rise in the cancer death rate of the negro during the past 30 years; (2) negro women show a much greater liability than white women, to malignant and benign tumors of the generative organs and also of the breast; (3) the prevailing rate of cancer of the skin is 3 times higher in whites than in negroes.

It is, of course, manifestly inadequate to select three terse statements such as the above from an essay packed with information; but for our immediate inquiry it is sufficient to know that Hoffman is strongly inclined to believe that available statistics seem to support the opinion that the colored races are less liable to skin cancers, because of the protective influence exercised by the pigment of the skin.

Heller, in his study of cancer in tar and mineral oil workers in the United States, found a very low incidence of the disease. In part, he attributes this to the fact that the negro workers in this industry possess at least a partial immunity to skin cancer. This assumption carried with it, of necessity, the conclusion that the carcinogenic effect of tar is, in part, at least, dependent upon the activating influence of light.[1]

In the clinic of The Barnard Free Skin and Cancer Hospital of St. Louis, we have made no special survey, but it is the unanimous opinion of all the workers in this institution that although breast and visceral cancer is very common in the negro, strikingly few patients with skin cancer have been seen during the past 25 years.

Up to this point, we have considered only those investigators, who have contented themselves with formulating experimentally uncontrolled hypotheses regarding the influence of light on the development of cancer. It has, of course, been recognized for years that the carcinogenicity of actinic rays could not be accepted on any other than experimental proof. Considering the importance of light as a possible factor in cancer, one is struck by the scanty effort devoted to the experimental study of this topic.

Grynkraut makes a contribution which seems to have the flavor of research, but which in reality is only a theory built up on an intricate bit of hypothetical reasoning involving exogenous and endogenous light rays (the latter corresponding to the so called mitogen-

[1] Heller does not furnish any grounds for believing that the negro enjoys any other special immunity not shared by white workers.

etic rays of Gurwitsch and a hypothetical *sensibilisateur*, which permits the utilization of light, and puts the cell nuclei in resonance with the wave length.

Bachem and Reed developed a method of measuring the transmission of light rays through tissues, thus facilitating the study of the problem of penetration. The method depended essentially on filtering the rays of a Kromayer lamp, an incandescent bulb, and infra-red radiation. These authors concluded from their studies, that the visible and near infra-red rays are strongly absorbed in the blood of the corium and subcutaneous layers; that the infra-red has very little penetrating power, not much of it going beyond the epidermis; and that variation in percentage penetration is greater in the ultraviolet than in other portions of the spectrum. At 280 millimicrons, absorption is marked in the corneum and prickle cell layer. On both sides of the band near 300 and 250 millimicrons, the penetration is greater, reaching the stratum malpighii and corium. From 250 millimicrons down, the absorption is so complete as to prevent any radiation from reaching the living layers of the skin. These authors believe that the strata corneum and granulosum must play an important part in light protection in lower sensitive layers.

The lipids, and in particular cholesterol, have assumed an increasingly prominent rôle in the story of cancer genesis. Roffo, who has probably done the largest amount of work in this particular field, believes that the lipids exercise a strong influence in preparing the terrain for cancer growth. More than this, he correlated the greater frequency of cancer of those regions of skin exposed to light with the increased cholesterol content of the exposed areas. Rats exposed to the sun developed a larger percentage of cholesterol than did control animals. Roffo also reports observations to prove that in cancer and precancerous lesions there is an hypercholesteræmia, with localization of cancer in the regions showing highest percentages of cholesterol. He believes that a relationship exists between the photoactivity of cholesterol and cell function, that sunlight serves to fix the cholesterol in the tissues, and that cholesterol then becomes an organic accumulator of light. The cholesterol becomes photoactive as a result of oxidation by light, the intensity of the oxidation depending upon the length of irradiation. Irradiation produces molecular changes, the molecular weights varying according to the duration of radiation.

One hesitates to accept some of Roffo's conclusions regarding the specific agency of cholesterol in cancer; and this hesitancy becomes all the more pronounced if one believes with Bishop that "our knowledge of the factors that determine the level of the various lipoid constituents in the blood in disease is pitifully meager. There is no evidence to support the suggestion of abnormal cholesterol conditions in association with cancer." Any one who carefully surveys the literature of tar cancer must be struck by the conflicting reports regarding the stimulating or inhibiting effect of lanolin, whether applied at the tarred site or remote to it. These conflicting reports incline one to be skeptical of Roffo's conclusions. Downes, in a study of 63 cases of malignant tumors, could find neither a constant relationship between the concentration of cholesterol in whole blood and plasma, nor any increase above normal of the blood cholesterol in the presence of cancer. Klaus reports a lowering of blood cholesterol in genital cancers in women. Thus, the reports vary all the way from hypocholesteræmia to hypercholesteræmia, rendering the topic one of utter scientific chaos.

Unfortunately, we encounter a somewhat similar state of affairs in the published experimental data dealing with the carcinogenic power of the ultraviolet rays of the spectrum. There seems to be no doubt that ultraviolet light is a factor in initiating skin cancers, but there is a clear cut conflict of opinion as to whether or not these rays serve to hasten the process of cancer development in mice that have been tarred.

Findlay (7) impressed by the citations in the literature of the high incidence of skin cancer in sailors, bargemen, fishermen, lightermen, farmers, gardeners, and graziers, in America, England, France, Italy, and Australia, concluded that even if the statistical value of the various reports were not high.

they nevertheless suggested strongly that sunlight and ultraviolet light may play an important part in the genesis of cancer.

In order to check this assumption, Findlay exposed mice to the rays of a quartz mercury vapor lamp. His conclusions were: (1) Exposure of mice to ultraviolet rays for a period of at least 8 months, caused the development of papillomata and epitheliomata (malignant) of the skin. (2) When mice were tarred and exposed to ultraviolet light, the period necessary for the induction of cancer was shorter than when either tar or violet ray exposure was used alone. (3) A series of 20 mice, tarred for one month, did not develop cancer, but in a similar series, tarred and exposed to ultraviolet light at the same time, 3 mice developed cancers.

In a later paper, Findlay reported the development of cancer in rats following exposure to ultraviolet light. The period necessary for induction of the cancers in rats was 21 months, in contrast with 8 months in mice, but Findlay attributes the increased time element to the species difference rather than to the nature of the stimulus.

Herlitz, Jundell and Wahlgren, exposed 27 mice to ultraviolet rays for 1 to 2 hours every 1 to 3 days for 7½ months (quartz lamp, 70 centimeters distance). After 200 days, 17 mice were alive and all of them showed one or more skin tumors, most of which were carcinomata. A group of control animals showed no tumors.

Putschar and Holtz exposed 57 rats, day and night, to ultraviolet rays, at a distance of 60 centimeters. After a period of more than 6 months, 13 of the 35 living animals developed malignant new-growths. These authors question the accuracy of Findlay's observations because of his much shorter exposures.

Rathman and Bernardt also question Findlay's conclusions, and report that using rabbits, they were not able to produce experimental cancer after 9 months of daily exposure to ultraviolet rays.

Kohn-Speyer reached the conclusion from her experiments that irradiating mice with ultraviolet light, as an adjunct to tarring, does not produce tumors (warts) more quickly than does tarring alone. She is unable to explain the discrepancy between Findlay's and her findings, but suggests that Findlay's rested on some, as yet undetermined cause, other than ultraviolet radiation alone.

There remains for discussion the work that has been done in natural light, in light in other than the violet end of the spectrum, and in the absence of all light. With the exception of the clinical observations of the supposed relationship between sunlight and skin cancers, which we have already noted, and the work of Roffo on the carcinogenic potency of photoactive cholesterol, which we have also discussed, very little work has been done with pure sunlight. Neumann, in an experimental study of tar cancer, merely mentions the fact that animals (mice) exposed to "intense illumination" showed no greater tendency to develop malignant tumors than did those that were kept under ordinary conditions

From what we know of the rôle that light plays in some of the diseases of metabolism, and from what we know of the clinical effects of light deprivation, it is not difficult to imagine that this same agency may be a factor in the origin and growth of cancer. A recent paper by Dodds calls attention to some of the work done by Warburg, illustrating by "a remarkable observation" the influence of light on the process of cell respiration: "if a slice of tissue is poisoned with carbon monoxide (CO) gas, cell respiration is strongly inhibited in the dark, but reappears when the tissue is brightly illuminated."

It is, of course, self-evident, that one of the approaches to the problem of light as a carcinogenic agent, lies in the direction of determining the effect of its total exclusion. The value of such an approach, it seems to us, lies in large part, in securing total darkness in the photochemical sense. Animal experimentation under such conditions is not easy of accomplishment. Marsh emphasizes this when he calls attention to inadequate ventilation and high temperature, as compromising features of his experiments. Dodds (who kept his mice in individual darkened cages) reports that mice can develop tumors in darkness, but by his own statements, he admits that his cages were "nearly light tight" and that the darkness in the cages was "all but complete." If we are testing the effect of absence of light,

then light must be absent and not partially absent. In Part I of this paper, we have described in detail how exclusion of light may be accomplished without in any other way interfering with the routine life of mice.

In addition to Dodds, the following workers have studied the effect of absence of light: Bang, Lipschuetz, Schorr and Ssobolewa, and Vlès, De Coulon, and Ugo. Half of these workers report that complete darkness exercised no influence on the development or growth of tar cancers, whereas the other half report that darkness tends to inhibit the development of tar cancers. Bang mentions, incidentally, that mice kept in complete darkness develop cancer as rapidly as do control animals. Unfortunately, he furnishes no information as to what constitutes *obscurité complete* in his experiments, how many animals he used in his light experiments, or what were his criteria of malignancy. The fact that, in all his experiments (including the ones done in darkness), he secured 115 cancers in 263 mice, arouses the suspicion that what he called cancer would not be so classified in our laboratory. Bang's work leaves a residuum of doubt on several counts, and leaves room for confirmatory work.

Lipschuetz is very definite in his statement that he worked in a well constructed photographic dark room, though no mention is made of means of regulating temperature or ventilation. He found that darkness played no inhibitory rôle in the development of pigment (melanomata) in his tarred mice. But here again one is left in reasonable doubt regarding the significance of darkness in the development of tar cancer, because Lipschuetz was exclusively studying pigment formation, and in black and gray mice.

Schorr and Ssobolewa divided tarred white mice and mice with transplanted tumors into groups (14 to 58 mice in a group) and subjected each group to varying light conditions, which were maintained during the process of tarring. They concluded from their experiments that light cannot be disregarded as a factor influencing the development of experimental cancer. Absolute darkness seemed in some instances to have no effect, but as a rule, darkness and also exposure to blue rays retarded the development of cancer and also lessened the tendency of the tumors to ulcerate. In spite of repeated careful reading of the article by Schorr and Ssobolewa, we could not determine how they excluded light, nor how efficiently it was excluded.

Vlès, De Coulon, and Ugo merely make the unsupported statement that when mice were kept in close confinement in dark cages, a retardation in the development of cancer in the tar painted animals occurred. Naturally, one has difficulty in determining just how to evaluate such a statement.

The conclusion that one must almost inevitably draw from a survey of the literature on light as a carcinogenic factor, is that more direct experimental evidence and data must be furnished if one hopes either to confirm the hypotheses that have been put forward, or to evaluate the worth of conflicting conclusions that have been drawn from experimental data. With such an object in view, the experiments detailed in Part I of this paper were planned and executed.

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THE RESISTANCE OF HEALING WOUNDS TO INFECTION

JEAN JACQUES DuMORTIER, M.D., BOSTON
Laboratory for Surgical Research, Harvard Medical School

THE purpose of this experimentation was to determine the degree of infectibility of simple incised and sutured wounds subsequently swabbed with a culture of pathogenic organisms after various intervals of time.

Howes, Sooy, and Harvey studied the rate of healing of clean, incised, sutured wounds in dogs by mensuration of the tensile strength of these wounds at definite intervals. They concluded that there exists a quiescent phase or "lag period," of from 4 to 5 days, characterized by "fibrin formation in the blood or plasma exuded between the surfaces of the fresh wound." During this interval, the approximation of the incised tissue is dependent upon the mechanical coaptation of its sutures. From the sixth day on, however—"the period of fibroplasia, manifest by multiplying fibroblasts and sprouting blood vessels"—the wound rapidly develops intrinsic holding power until, from the tenth to the fourteenth day, its tensile strength reaches a maximum, comparable to that of unincised tissue.

Carrel (3) studied the mechanisms of the repair of surgically aseptic cutaneous open wounds in dogs, by measurement of the variations in their dimensions. He showed that there is a quiescent period lasting from 1 to 5 days, during which the dimensions of the wound do not vary. This is followed abruptly by a period of "granulous retraction." The rate of reparation of the granulous period is directly proportional to the size of the wound. The end of this period coincides with the beginning of the period of epidermization which is inversely proportional to the dimensions of the wound. This period is succeeded by the period of cicatrization, of considerable length, during which progressive enlargement of the scar occurs. In a later report, Carrel and LeComte Du Noüy (4) state that the latent period of cicatrization in dogs varies generally from 5 to 7 days. It stops abruptly and contraction starts with maximum velocity. Carrel and Hartmann (5) found, in subsequent experiments, that when a surgically aseptic open wound becomes infected, arrest or regression of the repair occurs, yet the senior author states that the application of turpentine, chick embryo, and staphylococci decreases markedly the length of the latent period, often to less than 2 days. This work is of considerable interest in relationship to our findings.

Billroth, one of the first to make a study of wound infections, demonstrated that granulating surfaces offer considerable resistance to infection. Virulent organisms, implanted on granulating tissues of dogs, cause no infection, but these same bacteria inoculated into fresh wounds result in extensive infection, in some instances leading to the death of the animal. He believed that this resistance of granulation tissue is due to lack of lymphatics. Noetzel and Afanassieff, working on absorption of poisons from granulating tissues, both independently, came to the conclusion that granulation tissue affords considerable protection against the invasion of bacteria. Halley, Chesney and Dresel, demonstrated that granulations constitute a relatively unfavorable environment for the survival and growth of Streptococcus erysipelatis and Staphylococcus aureus.

It is a clinical truism on the other hand that fresh wounds are readily infected. In 1897, Schimmelbusch and Ricker showed that there is rapid absorption of both pathogenic and saprophytic bacteria from fresh bleeding wounds. W. H. Welch states: "The period during which the rapid absorption of bacteria from a fresh wound takes place is of short duration. As soon as a coagulum has formed on the surface of the wound, the open mouths of lymphatics and blood vessels are plugged, the conditions have changed and fine particles like bacteria are no longer quickly transported into the intact lymphatics and blood circulation. The surface of a healthy granulating wound offers great resistance to the invasion

of bacteria, almost as much as an intact exposed surface of the body. Slight injuries, such as probing, removal of dressings and other manipulations may convert a granulating surface into a fresh wound with accompanying dangers of infection."

However, from an experimental point of view that period in which an operative incision changes from an excellent locus of infection to one offering protection comparable to that of intact epidermis is not known. That period in healing, in which a wound may be manipulated without danger of resulting infection through surface implantation of organisms, whether by wilful or unintentional abandonment of the principles of asepsis, has not been demonstrated.

PROCEDURE

From the Surgical Wards of the Peter Bent Brigham Hospital a 24 hour broth culture of Staphylococcus aureus hæmolyticus was obtained from an abscess of the buttock; 0.5 cubic centimeter of this culture was injected subcutaneously into each of four guinea pigs, and in three days, all developed typical abscesses. Smears of the pus demonstrated the organisms in pure strain. This strain was kept on plain agar and its virulence maintained and checked by weekly inoculations into guinea pigs. Six hours prior to its experimental use, it was transferred to dextrose infusion broth, 0.5 cubic centimeter of this 6-hour broth culture being used in each of the experiments.

The operative technique in all experiments was the same. The abdomen of each pig was widely shaved and cleansed with green soap and water. The operative field was carefully prepared with 70 per cent alcohol and bichloride of mercury (1:4000). The abdomen was draped in the usual manner. Under ether anæsthesia an incision 5 centimeters in length was made through the skin, subcutaneous tissue, and abdominal musculature. Hæmostasis was assured. The musculature was then carefully approximated with interrupted fine black silk sutures, and the skin closed in like manner, care being taken to leave no dead spaces or gaping edges. A sterile dressing was applied and kept intact with adhesive, simulating Montgomery straps. These were found very satisfactory and anchored the dressing down tightly. To guard further against contamination of the wound, the animal's legs were fastened with rubber bands, which necessitated the maintenance of a dorsal position.

Thirty incisions were made in each series of experiments, except the first, in which forty-two were made. In the first series no organisms were implanted; in the second, immediately at the close of operation 0.5 cubic centimeter of a broth culture of Staphylococcus aureus hæmolyticus obtained as described above was gently swabbed along the operative site, and a sterile dressing applied; in the third, 2 hours were allowed to elapse before the sutured wound was similarly treated; in the fourth series, 6 hours; in the fifth, 12; in the sixth, 24; and then 24 hours later in each subsequent series. Control experiments were performed both independently and in conjunction with each series as to the virulence of the organisms, the resistance of the intact skin to resist these organisms, and on the ability of the uninoculated wound to heal by first intention.

RESULTS

1. Operative incisions in guinea pigs, made and followed with aseptic technique, heal by first intention. In 42 operative procedures, 41 wounds healed without infection. One developed a small stitch abscess on the fifth day. Stitches were removed routinely on the sixth day, and on the eleventh day the scars were scarcely discernible.

2. Staphylococcus aureus hæmolyticus implanted upon the intact skin does not cause infection. The organisms were smeared on the shaved abdominal wall of forty guinea pigs. No infection occurred.

3. In the first series of 30 animals, Staphylococcus aureus hæmolyticus was implanted along the line of closure *at the completion of the operative procedure*. Within 4 days gross infection was present in all cases. Four guinea pigs died of overwhelming infection within 3 days; 3 had extensive spreading infections of the anterior abdominal wall; 20 developed gross abscesses in the subcutaneous

tissue and muscle layers; and 3 an accumulation of suppurative fluid beneath the skin. Microscopic sections confirmed the gross findings. Gram stains revealed staphylococci in great numbers. The three control incisions healed without infection.

4. In the second series Staphylococci aureus hæmolyticus were implanted upon the sutured wound *2 hours after operation*. Gross infection was apparent in all incisions within 4 days. Five guinea pigs died of overwhelming infection within 3 days. Two developed an extensive spreading infection of the anterior abdominal wall. Twenty-two had gross abscesses, and one an accumulation of suppurative fluid beneath the skin. The controls were uninfected. Their findings were substantiated by microscopic examinations. Large numbers of staphylococci were found in all inoculated incisions.

5. In the third series, staphylococci were implanted upon the sutured wound *6 hours after operation*. Infection was present in all incisions within 4 days. One pig died of overwhelming infection within 3 days. There were no extensive infections of the abdominal wall. Twenty-eight incisions developed gross abscesses. One incision showed no evidence of infection grossly, but microscopic examination revealed its presence. The control incisions healed by first intention. The organisms were found in large numbers in all the infected wounds. In general, the infections were less extensive in this series than in the two preceding ones.

6. In the fourth series, staphylococci were implanted upon the sutured wound *12 hours after operation*. Infection was present in 83 per cent of the incisions within 4 days after implantation of the organisms. There were no deaths and no extensive infections in contrast to the previous series. Twenty-one incisions contained gross abscesses. Microscopic evidence of infection was found in four incisions though not manifest grossly. Five (17 per cent) showed no gross or microscopic evidence of infection. The control incisions healed *per primam*. The organisms were demonstrated in all the infected wounds. There was a marked decrease in the severity of infections in this series.

7. In the fifth series, staphylococci were implanted upon the sutured wound *24 hours after operation*. Infection was present in 66 per cent of the incisions within 4 days, after the implantation of organisms. There were no deaths and no extensive infections. Fifteen wounds had gross abscesses; only one of which was at all severe. Staphylococci were present in these lesions. Five showed unmistakable evidences of infection microscopically, which was not apparent grossly. In 4 of those incisions demonstrated to have infection only by microscopic means, no organisms were found. Ten incisions (33 per cent) were healing *per primam intentionem*. The controls were negative.

8. In the sixth series, staphylococci were implanted upon the sutured wound *2 days after operation*. Infection was present in 56 per cent of the incisions within 4 days after the implantation of organisms. There were no deaths and no extensive infections. Thirteen incisions were found to have gross abscesses, two of which were severe. Four incisions showed no gross evidence of infection, but microscopic sections revealed its presence. Thirteen incisions (44 per cent) were healing by first intention. Staphylococci were present in all the gross lesions, and in 3 of the 4 microscopic lesions. The controls were negative.

9. In the seventh series, staphylococci were implanted upon the sutured wound *3 days after operation*. Infection was present in 36 per cent of the incisions within 4 days after the implantation of organisms. Six incisions contained gross abscesses, in all of which staphyiococci were found. None of these abscesses were over 0.5 centimeter in diameter. Five wounds showed evidence of infection on cut section although not visible grossly. In 2 of these staphylococci were identified. Nineteen incisions (64 per cent) showed no evidence of infection. The controls were negative.

10. In the eighth series, staphylococci were implanted upon the sutured wound *4 days after operation*. Infection was present in 10 per cent of the incisions within 4 days after the implantation of organisms. One incision was found to have a gross abscess 0.1 centimeter in diameter in which the staphylococcus was identified. Two showed unmistakable

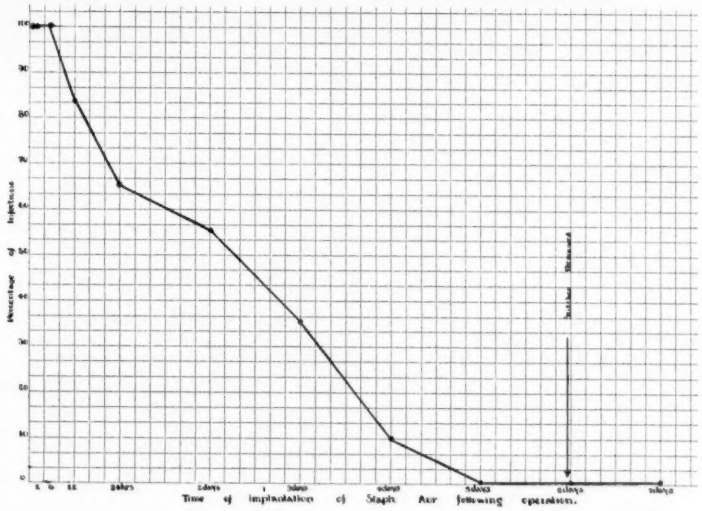

Fig. 1. Curve showing relationship of infection to time of implantation of organisms in sutured wounds.

evidence of infection microscopically but not grossly. No organisms were shown in these two sections. Twenty-seven (90 per cent) healed by first intention. The controls were negative.

11. In the ninth series, staphylococci were implanted upon the sutured wound *5 days after operation*. Gross and microscopic examination revealed no infection.

12. In the tenth series, staphylococci were implanted upon the wound *6 days after operation*, immediately following the removal of all skin silks. No infections could be demonstrated either grossly or microscopically. In 7 instances, the wound was partially reopened while pulling out the stitches, and the organisms were swabbed into the defect without resulting infection.

13. In the eleventh series, staphylococci were implanted upon the wound 7 days after operation and 24 hours following the removal of the skin silks. No infections could be demonstrated either grossly or microscopically. On the eleventh day after operation, when the wounds were examined, it was only with difficulty that the operative incision could be identified.

DEDUCTIONS

These results demonstrate that after an incision of tissue, there follows a well defined period about 6 hours in length in which that tissue's resistance to invasion by bacteria is at a minimum. In this period, bacteria not only flourish and cause suppuration in the local lesion, but invade, without apparent restraint, the environing tissues, setting up extensive, rapidly spreading infections, which, in a number of instances, result in the death of the animal. After this period, however, the factors concerned in the repair and protection of tissue become increasingly apparent. When organisms are implanted upon a sutured wound 12 hours after operation, although the great majority of incisions become infected (83 per cent) the infections are localized. No systemic infections develop, which overwhelm the animal, and no extensive spreading suppuration occurs. From this time on, the percentage and severity of infections steadily decreases (see Table I) until, between the fourth and fifth post-operative days it is no longer possible to cause infection by implantation of virulent organisms on the surface of the wound (see graph).

This period of from 4 to 5 days coincides with the "lag period" of healing wounds, described by Harvey (7) and by Carrel (3), and which Harvey points out is common to all growth phenomena. This period is charac-

TABLE I.—DURATION OF INFECTION

Degree of infection	Time of implantation of Staphylococcus aureus following operation.										
	0	2 hr.	6 hr.	12 hr.	24 hr.	2 days	3 days	4 days	5 days	6 days	7 days
Severe	21	25	17	7	1	2	0	0	0	0	0
Abscess 1.0 cm. in diameter	5	2	7	0	0	2	0	0	0	0	0
Abscess 0.5–1.0 cm. in diameter	1	3	8	5	4	4	3	0	0	0	0
Abscess 0.2–0.5 cm. in diameter	3	0	2	8	8	3	1	0	0	0	0
Abscess 0.1–0.2 cm. in diameter	0	0	1	1	2	3	2	1	0	0	0
Microscopic only	0	0	1	4	5	4	5	2	0	0	0
None	0	0	0	5	10	13	19	27	30	30	30
Total infections	30	30	30	25	20	17	11	3	0	0	0
Percentage infections	100	100	100	83	66	56	36	10	0	0	0

terized by "fibrin formation in the blood or plasma exuded between the surfaces of the fresh wound." This "fibrin formation" apparently has but little resistance against the invasion or multiplication of bacteria and it is only when it has been replaced by fibroblasts that protection against bacterial invasion becomes complete. It would seem, therefore, that resistance to infection is not complete, until the lag period of a healing wound (4 to 5 days) has been succeeded by what Harvey speaks of as the period of fibroplasia—manifest by "multiplying fibroblasts and sprouting blood vessels."

It is of clinical importance that for the first 5 days following an operative incision, extreme care be taken in the manipulation of a wound, as during this period, infection is possible from implantation of virulent organisms on its surface.

On first thought it might seem surprising that when virulent organisms are implanted along a wound, on the sixth day, immediately following the removal of stitches, no infection results. However, upon consideration that these stitches have become "walled off" by granulation tissue, which is highly resistant to the invasion of bacteria, it is readily understood. Even in those instances in which, due to a sudden movement of the animal while removing a stitch, a small segment of the wound was reopened, no infection developed, although the organisms were swabbed into this defect. This is likewise explainable upon the same factor of resistance of granulation tissue to the invasion of bacteria.

SUMMARY

1. The resistance of a healing wound to infection is minimal during the first 6 hours.

2. After the first 6 hours, infections decrease in number and severity until fifth day.

3. On the fifth day after operation, the resistance of a wound to infection has reached a level comparable to that of intact tissue.

4. Removal of stitches on the sixth day after operation does not lower the resistance of the wound to infection.

5. The period of infection corresponds to the "lag period" of healing wounds.

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THE SURGICAL REMOVAL AND HISTOLOGICAL STUDIES OF SYMPATHETIC GANGLIA IN RAYNAUD'S DISEASE, THROMBO-ANGIITIS OBLITERANS, CHRONIC INFECTIOUS ARTHRITIS, AND SCLERODERMA

WINCHELL McK. CRAIG, M.D., F.A.C.S., ROCHESTER, MINNESOTA
Division of Surgery, The Mayo Clinic
JAMES W. KERNOHAN, M.D., ROCHESTER, MINNESOTA
Section on Pathologic Anatomy, The Mayo Clinic

THE surgical removal of sympathetic ganglia has been followed by relief of symptoms in selected cases of Raynaud's disease (2), thrombo-angiitis obliterans (3), chronic infectious arthritis (19), and the acral type of scleroderma (4), but studies of the ganglia removed have been inadequate to determine the presence of any constant histological changes.

Operations consisting of the removal of ganglia have stimulated interest in the clinical, physiological, and pathological aspects of the sympathetic nervous system. This study is based on 208 cases in which the cervicothoracic sympathetic ganglia were removed to obtain sympathetic denervation of the upper extremities, and the second, third, and fourth lumbar sympathetic ganglia were removed to obtain sympathetic denervation of the lower extremities. In all cases, removal of the cervicothoracic ganglia was carried out according to the technique described by Adson (1), consisting of posteromedian incision over the lower cervical and upper thoracic vertebræ, followed by the bilateral removal of the transverse process and a portion of either the first or second rib, permitting entrance into the posterior mediastinum, and access to the cervicothoracic sympathetic trunk. The lumbar sympathetic trunk was removed through a median abdominal and bilateral transperitoneal incision, the second, third, and fourth sympathetic ganglia on both sides at the same operation (2) being removed.

In a certain number of operations for the removal of sympathetic ganglia, indications of inflammatory reaction in both the posterior mediastinum and in the postperitoneal tissues were found. In the abdomen, enlarged lymph nodes frequently interfered with the exposure of the sympathetic chain to such an extent that it was necessary to dissect and remove them before the operation could be completed. Although enlarged lymph nodes were not encountered in the posterior mediastinum, the difficulty of dissecting the sympathetic trunk due to adhesions suggested the presence of mild mediastinitis. These observations at operation raised the question of local inflammatory reaction playing some part in the dysfunction of the sympathetic system, by involving the ganglion tissues and cells. Consequently we have been making a study of the ganglia removed at operation and not only have examined them histologically but have cultured them on different mediums to investigate possible bacterial invasion. The ganglia which have been removed have been kept sterile, emulsified, and cultured in glucose brain broth and brain agar. In only a few instances have there been any positive cultures and these Rosenow reported as consisting of pleomorphic streptococci.

The local inflammatory reaction about the sympathetic ganglia in the operative cases aroused our interest to such a point that observations were made in 40 non-operative cases at postmortem, in which derangement of function of the sympathetic nervous system had not been apparent. It was surprising to find that in a large percentage of these cases the lymph nodes lying postperitoneally along the vertebral column and superimposed on the lumbar sympathetic chain were enlarged and simulated the picture seen at operation, but this could not be established as an inflammatory process.

In order to correlate the clinical, surgical, and pathological aspect of these cases, we have tabulated our histological observations to correspond to the clinical diagnoses, and

although all the ganglia have been investigated, we are presenting four clinical histories from the entire group of cases as a background of our pathological considerations. These cases have been chosen not only because they represent the diagnostic groups, but also because they responded exceptionally well to the therapeutic application of sympathetic ganglionectomy. Therefore, any pathological changes occurring in the ganglia should have been evident in these cases.

In the cases of Raynaud's disease, 50 were submitted to operation; in some of them bilateral lumbar ganglionectomy, in some bilateral cervicothoracic ganglionectomy, and in others both operations were done.

RAYNAUD'S DISEASE

This disease occurs in adult life, predominating in women, and is characterized by the presence of symmetric changes in the color of the hands and feet or of the fingers and toes. It may involve the upper or lower extremities, and occasionally the nose and the lobes of the ears. The blanching of the skin is brought about by vasoconstriction of the vessels, due to exposure to cold or emotional influences. This blanching is followed by cyanosis, which continues until the vasoconstriction subsides. In the earlier stages of the disease, this subsidence is accompanied by discomfort, then by aching, and finally by severe pain. As the disease progresses, the changes in color become more prominent and the skin remains more or less cyanosed unless the condition is relieved by the application of heat externally. Should the vasoconstriction become prolonged and the circulation markedly decreased, gangrene may occur. Gangrene in Raynaud's disease differs from the gangrene which occurs when the vessels are occluded, in that it produces dry ulcers at the tips of the fingers or toes with distorted growth of the nails, instead of complete gangrene of one of the digits. If the process is allowed to continue, the gangrene will ascend and will become extremely painful. Usually the patient complains of subjective numbness, which interferes with the function of the extremity and adds to the general discomfort and incapacitation. The disease does not always progress to the severe forms; hence the milder forms may be controlled by changing occupation or climate. When the symptoms persist, and ulceration and gangrene develop, operation should be performed. In almost all the cases in which operation has been performed, the relief of pain is almost instantaneous, the cyanosis disappears, and the skin becomes warm, pink, and dry; the ulcers heal, the nails take on normal growth, and the patient is restored to normal health.

Illustrative case. A woman, aged 25 years, gave a history of blanching of the right index finger 3 years previous to registering at The Mayo Clinic; this came on during the winter months, but disappeared in summer. The next winter, however, the condition became gradually worse, both hands becoming cyanotic to the wrists, associated with numbness and dull aching pain. This did not clear up with the advent of warm weather, and the following winter small dry ulcers developed in different finger tips, and the feet also began to manifest the symptoms of color changes and pain when exposed to cold.

General examination was essentially negative except for marked vasomotor changes in the extremities. A diagnosis of Raynaud's disease was made, and because the hands were more involved than the feet, cervicothoracic sympathetic ganglionectomy was performed. The stellate and second thoracic sympathetic ganglia were removed from both the right and left sides (Fig. 1). The patient's convalescence was uneventful and she was completely relieved of cold, blue, numb hands; 15 days after operation, the ulcers on the tips of the fingers had completely healed.

An interval of 6 weeks was allowed to elapse before operative interference to relieve the lower extremities was thought advisable. The patient's complaint concerning her feet was similar to that concerning her hands in that there were marked grades of cyanosis on exposure to cold, mild pain, numbness, and tingling followed by periods of recovery during which there was burning, redness, and sweating. The symptoms were completely relieved after bilateral lumbar sympathetic ganglionectomy at which time the second, third, and fourth lumbar sympathetic ganglia were removed on both sides (Fig. 1).

In these, as in all the other ganglia removed, various points were noted. The blood vessels showed a mild degree of thickening of the wall with subsequent narrowing of the lumen so that the ratio of lumen to wall which is normally 2 to 1 in small arteries was now only 1.7 to 1. In addition in a few arterioles, there was an increase in prominence of the lining endo-

thelial cells, but this was by no means universal and was present only in a mild degree. There was no evidence of acute or chronic inflammation; there were no fibroblasts or increase in the connective tissue as shown by the van Gieson stain, and polymorphonuclear leucocytes were not present. Although there was no inflammation, lymphocyte-like cells were present, and these were in two small groups and not scattered diffusely throughout the ganglia. At one end of the ganglia there was slight œdema of the connective tissue. This varied greatly in the various ganglia removed for this condition and was never pronounced. Besides the stains used as a routine, thionin stain, Orlandi silver impregnation method, Hortega's silver carbonate method, and Cajal's gold chloride and sublimate method were employed in the study of the ganglion cells. In the case under consideration there was little change in any of the cells other than that seen normally. There was slight chromatolysis in less than a third of the cells and slight vacuolization in the periphery of some of the others; this was not advanced and was present in about half of the cells. In the same cells, some of the endocapsular cells were prominent, and the vacuoles in the periphery of the ganglion cells appeared to be caused by swelling of the endocapsular cells. Some of the capsular cells thus appeared as deep-staining nuclei with clear spaces around them, causing excavations of the cytoplasm of the underlying ganglion cells. Only occasionally was there any demonstrable increase in the ectocapsular cells. The various special stains were unsatisfactory in demonstrating the bodies of the endocapsular cells. In a seventh of the ganglion cells pigment granules were not present, whereas in about five-sevenths a slight amount was present (graded 1), and in the remaining seventh there was considerable pigment (graded 2). This is a normal phenomenon and is seen constantly in increasing amounts in normal ganglia with advancing age. In ganglia removed from patients with Raynaud's disease, in the group in which there was no pigment, the average age of the patients was 24.3 years, in the group in which pigment was graded 1, the average age was 33.7 years, and in the group in which it was graded 2, the average age was 40 years, thus conforming to the tendency for increased pigment deposition in many nerve cells, especially sympathetic ganglia with advancing age. There is, in any control series of ganglia, a marked variation in pigment precipitation, but it is almost always more abundant in the ganglion cells of older persons than in those of younger persons.

THROMBO-ANGIITIS OBLITERANS

There were 97 patients with thromboangiitis obliterans on whom the cervicothoracic or lumbar ganglionectomy or both types of operation were performed, and the ganglia removed were studied histologically.

Thrombo-angiitis obliterans occurs in adult life, has a predilection for men, and affects persons of all races, in spite of the fact that it formerly was supposed to occur more commonly among Jews. The underlying causes have not all been determined. The disease seems to progress after infection of the inner walls of the arteries and formation of a clot which occludes the vessels, thus decreasing the blood supply to the extremity. The infection and the formation of the clot vary in degree and distribution. The condition may affect the distal part of one principal artery, or it may include all the principal arteries of all extremities at different periods. The usual course of this disease is rather slow; the main vessels of the feet and legs become involved early and those of the upper extremity later. When it is economically possible, relief can be obtained by discontinuing work, remaining at rest in bed, applying heat to the extremities, and being treated with vaccines administered intravenously. In time, organization of the intravascular clot takes place and circulation is restored. However, many patients are compelled to work, subjecting their hands and feet to trauma, and ulcers may develop sooner or later and refuse to heal. These ulcers become infected, the infection spreads to the adjacent tissues, and more thrombosis and gangrene appear, necessitating amputation of the extremity (9). By means of operations on the sympathetic system, it is possible to relieve the vasomotor spasm of the col-

lateral vessels, which improves circulation, tends to prevent ulceration, infection, and gangrene, and hastens healing of existing ulcers and abrasions. In suitable cases selected by means of the various tests of altered vasoconstriction [Brown's "fever test" (7), White's (22) diagnostic nerve block, and White (22), Morton and Scott's (16) spinal anæsthesia test], the temperature of the skin is increased from 2 to 10 degrees, depending on the amount of vasoconstriction present before the operation, the ulcers begin to heal, and the patient is restored to his former status as a wage earner. Moreover, the operation may prevent further gangrene and extension of the process to the opposite extremity, which usually is involved to a slighter degree than the extremity which causes the symptoms. Operation is not advised for milder cases, in which the patients are not inconvenienced greatly, are free from ulcers, and are able to carry on regular work under symptomatic treatment. The normal expectancy for amputation of one or more limbs in cases of thrombo-angiitis obliterans even under ideal conditions is more than 25 per cent, but there has been a definite reduction of this percentage in cases in which sympathetic ganglionectomy has been performed. Less than 5 per cent of the patients who have left the clinic following operations on the sympathetic ganglia have been obliged to submit to subsequent amputation (6). This comparison emphasizes the value of operations on the sympathetic system in protecting patients with thrombo-angiitis obliterans from losing one or more extremity by amputation.

Illustrative case. A man, aged 35 years, came to the clinic complaining of pain in the feet and legs associated with ulcers and cyanosis of the toes. His history dated back almost 12 years, when, after trauma to the right instep, he experienced intermittent pain in walking. Six years following this, cyanosis, rest pain, and ulceration in the right little toe developed, which proved very indolent to treatment. Five years after the trouble with the little toe began, a similar condition developed in both great toes and the ulcers remained open for several months. Following this, cyanosis occurred in both feet, and intermittent pain developed. Two months before registration at the clinic, the four lateral toes on the left foot became blue and cold, and ulceration occurred between third and fourth and fourth and fifth toes.

On examination the lower extremities were cold and blue. The femoral and popliteal pulses were present on both sides; the posterior tibial artery on the right was partially occluded and completely occluded on the left; both dorsalis pedis arteries were occluded. The right foot was cold and dark, but did not contain ulcers; the left foot was cyanotic, especially over the lateral portion, and indolent ulcers were present between the third and fourth and the fourth and fifth toes.

A diagnosis was made of thrombo-angiitis obliterans with vascular insufficiency. Intravenous typhoid vaccine was given which was followed by increase of surface temperature sufficient for a satisfactory vasomotor index. Bilateral lumbar sympathetic ganglionectomy was carried out, and the second, third, and fourth lumbar sympathetic ganglia were removed (Fig. 1). There was evidence of an inflammatory reaction about both sympathetic chains. The patient recovered uneventfully, and when seen almost a year after operation, he was working and was well satisfied with the result obtained in his case.

Histological study of the ganglia showed that there was more proliferation of the lining endothelial cells of the arterioles and small arteries than in the cases of Raynaud's disease which we have studied, but this proliferation was by no means universal. There was also slight thickening of the walls of the larger vessels present in the ganglia, so that the normal ratio of lumen to wall (2 to 1) was reduced to 1.8 to 1, and is thus less than that seen in the vessels examined in cases of Raynaud's disease. There was no evidence of acute or chronic inflammation. Fibroblasts were not present, and excessive connective tissue was absent, as demonstrated by special staining methods. Several small collections of lymphocyte-like cells were present, but none were scattered diffusely throughout the ganglia. The groups were not associated with blood vessels. There was mild œdema of the connective tissue, but this was not universal in the ganglia. The œdema was more marked in the ganglia removed from patients suffering from thrombo-angiitis obliterans than from any other ganglia studied. Special staining methods were employed in studying the ganglion cells themselves, but the changes that were present were very slight. There was a mild degree of chromatolysis in about a seventh of all the cells, whereas a fourth were normal. In more than half of the cells small vacuoles were present at the periphery, and these corresponded

in situation to the endocapsular cells. The vacuoles appeared to have been caused by swelling of the endocapsular cells, the nuclei of which were prominent, and cytoplasm could be demonstrated only with difficulty with the special stains; that is, Cajal's gold chloride and sublimate method and Hortega's silver carbonate method for microglia and oligodendroglia. The deep-staining nuclei were surrounded by a clear space such as is seen in acutely swollen oligodendroglial cells described by Penfield and Cone. Mucus stains revealed only slight traces of some of these vacuoles. There were several cells which had been replaced by large vacuoles, and remnants of the ganglion cells were compressed at one part of the periphery against the cell capsule. This process of vacuolar degeneration or destruction seemed to be different from changes brought about by swelling of the endocapsular cells. The swollen endocapsular cells corresponded closely to the vacuolization present in the periphery of cytoplasm of the ganglion cells. Pigment was present in the cytoplasm of more than 90 per cent of the ganglion cells, but was slight in amount in 75 per cent of the cells. There was considerable pigment in 20 per cent of the cells, and there were few cells in which there was pigment graded 3. The average age of the patients with thrombo-angiitis obliterans was 35.7 years. The average age of patients without pigment in the ganglion cells was 29.6 years, of those with pigment graded 1 the average age was 36.8 years, and of those graded 2 the average age was 46 years; the one patient with pigment graded 3 was aged 53 years. This again conforms with the tendency for pigment to increase with advancing age in nerve cells, and especially in the sympathetic ganglion cells.

ARTHRITIS

Ganglia from 46 patients with arthritis were studied histologically. In some cases both the upper or lower extremities were denervated, and in others all four extremities.

Among the various types of patients suffering from chronic infectious arthritis are young adults who have painful, swollen, tender joints, associated with limited motion, atrophy of the muscles, and loss of function. Patients complain also of cold extremities, mild changes in color of fingers and toes, and excessive perspiration. There is a tendency for the condition to progress slowly; it is not altered by removal of foci, immobilization, massage, or exercise, and is symptomatically relieved only by the application of various types of heat. In certain selected cases of this group, operations on the sympathetic ganglia are followed by relief of symptoms and by the improvement in circulation which follows the vasodilatation (20). The skin becomes warm and dry, and pain is generally relieved, the tenderness tends to disappear, and the swelling subsides. In selecting suitable cases for the operation, the rise in surface temperature of the extremity following intravenous administration of typhoid vaccine is used as an index, and if there is no appreciable rise in surface temperature or relief of symptoms following protein injections, the operation is not indicated.

The following case is reported because it presents the salient features of a slowly progressive arthritis not yielding to the usual therapeutic measures. The associated vasomotor changes, as evidenced by the cold clammy extremities which were temporarily relieved by the intravenous administration of typhoid vaccine, formed the basis for sympathectomy. The history of psoriasis and the presence of mild lesions at the time of examination raised the question of a differential diagnosis of chronic infectious arthritis and arthropathia psoriatica (13). The clinical features, however, were those of the former and the excellent response to operation rendered this case most suitable for histological study.

Illustrative case. A man, aged 40 years, came to the clinic complaining of pain, stiffness, and deformity in the fingers and toes. Four years before admission, he began to have swelling, redness, and pain in the right index finger. The remaining digits of the right hand became similarly involved and gradually the left hand became affected with the same process. The condition progressed, and after 2 years had elapsed, the toes on both feet began to swell and to become painful and stiff. The arches ached with activity, but were relieved by rest. This condition progressed to the point where the patient was unable to walk or use his hands without pain and discomfort.

Examination disclosed areas of psoriasis on the upper midsacral regions and outer surface of the right leg which had been present intermittently for the previous 6 years. There was moderate swelling of the left wrist with tenderness and 20 per cent limitation of dorsal flexion. Both hands were cold and slightly clammy with swelling, and motion of phalangeal joints was limited. There were trophic changes in the fingernails. Both feet were cold and clammy. There was marked swelling and tenderness at the base of the toes on both feet, and tenderness on pressure over both arches. Both hands and feet were cyanotic. Roentgenograms revealed healed tuberculous lesions in the upper part of the right lung. One dead tooth was found, and removed. Mild prostatitis was treated. Because of the evident associated vasomotor spasm of the peripheral arteries, typhoid vaccine was given intravenously which was followed by marked relief of pain, and the skin over the extremities became warm and pink. When the surface temperature was compared with that taken before the injection had been given, a marked rise had taken place, thus establishing a satisfactory vasomotor index.

Bilateral lumbar sympathetic ganglionectomy (Fig. 1) was performed. The second, third, and fourth lumbar sympathetic ganglia were resected on both sides. There was a marked inflammatory reaction about the sympathetic chain and the overlying lymph nodes were enlarged and inflamed. The lymph nodes were removed and microscopic section revealed fatty fibrosis with inflammatory nodules. Following an uneventful convalescence, the patient was relieved of almost all the pain in both feet; they became warm and cyanosis disappeared.

The question of cervicothoracic sympathectomy was considered, but the patient wished to wait for time to evaluate the improvement in the lower extremities. Six months later examination revealed increased severity of the condition of the hands. The patient was walking without pain, his feet were warm and dry, and he requested that a second operation be considered. Bilateral cervicothoracic sympathetic ganglionectomy (Fig. 1) was done, removing the stellate and second thoracic ganglia after resecting the transverse process and part of the first rib. Marked alleviation of pain in both hands followed. After an uninterrupted convalescence the patient returned home, continuing to improve until he could use his hands without pain and with very little residual stiffness (15).

The changes observed histologically in these ganglia were similar to those described in the ganglia removed from patients suffering from Raynaud's disease and thrombo-angiitis obliterans. Most of the blood vessels were normal, but in a few there was mild proliferation of the lining endothelium of the intima, and in others there was slight thickening of the walls of the larger arteries in the ganglia. The ratio of lumen to wall in this group was 1.8 to 1, instead of the normal 2 to 1. There was no evidence of acute or chronic inflammation, polymorphonuclear leucocytes were not present, fibroblasts were absent, and there was no increase in adult connective tissue. Although there was no inflammation, there were small collections of lymphocyte-like cells, but these were collected in groups and not scattered diffusely throughout the ganglia. In the ganglia removed from patients suffering from arthritis slightly less than 50 per cent contained similar small collections of these lymphocyte-like cells. There was a slight amount of œdema in the ganglia, but it was localized, and varied greatly in the other ganglia removed for this condition. Special stains were utilized in studying the ganglion cells, and approximately two-fifths of the cells were normal; one-fifth of them manifested a mild degree of chromatolysis and a few cells were pyknotic. In approximately two-fifths of the cells there was vacuolization at the periphery, and this corresponded to what seemed to be swollen endocapsular cells. This vacuolization was mild in most of the cells in which it was present, but in a few cells it was quite prominent. The swollen endocapsular cells corresponded in situation to the vacuoles in the periphery of the ganglion cells. In an eighth of the ganglion cells pigment was not present in the cytoplasm, whereas in three-fourths there was a slight amount of pigment (graded 1), and in the remaining eighth, it was more pronounced (graded 2). The average age of the patients suffering from arthritis was 30.7 years. The average age of those whose ganglia contained pigment less than grade 1 was 19 years; of those with pigment graded 1, 31.9 years; of those with pigment graded 2, 35 years; and of the one patient whose ganglion cells contained pigment graded 3, the age was 53 years. These observations again support the opinion that pigment in sympathetic ganglion cells increases with age, and is not necessarily a manifestation of the disease process.

SCLERODERMA

Scleroderma is sometimes alleviated by sympathetic ganglionectomy. The condition

of the skin is characterized principally by brownish discoloration associated with thickening or atrophy, usually involving the fingers and toes. The distribution may be circumscribed, spotty, or diffuse, and limited to the feet and legs, or it may involve the hands, arms, face, and neck, and the skin over the upper part of the thorax. The muscles and bones may be included in the atrophic and degenerative process. The disease is usually slowly progressive, and it occurs at any age or among persons of either sex, but more frequently among young women. All cases of scleroderma do not result from disturbances in the sympathetic nervous system, but the lesions of the feet, legs, hands, arms, and face frequently are preceded by a phase of increased vasoconstriction characterized by cold, sweaty, bluish hands and feet, similar to those of Raynaud's disease(2). This type of scleroderma has been observed also in cases of thrombo-angiitis obliterans, and chronic infectious arthritis. The early cases of scleroderma, associated with vasomotor changes, sometimes respond satisfactorily to operation on the sympathetic nervous system, but in advanced cases there is no marked improvement, because of the pathological changes that have taken place in vessels, skin, and subcutaneous tissues (8, 17). The results in the early cases are those of immediate improvement in circulation, and loosening and thinning of the skin over the extremities, face, and neck. The skin and muscles of the face lose their drawn expression, the mouth can be opened more widely, and the tongue can be protruded. The operation will not help in advanced cases, in which thickening of the skin and hardness of the muscles have become extreme, and therefore, if operation on the sympathetic system is to be employed in the treatment of scleroderma of vascular origin, it should be employed as soon as the disease is recognized in order to prevent its progress. If the condition is permitted to continue, it usually results in pain, deformity, and total invalidism.

In 16 cases of scleroderma of the vasomotor type, operation has been done and sympathetic ganglia have been removed. The following case was selected from the group because of the history and definite improvement following operation. We have assumed that histological changes, if present, should be discernible in the removed ganglia of successful cases.

Illustrative case. A woman, aged 48 years, came to the clinic complaining of stiffness of the hands associated with thickening of the skin over the thorax and face. Her history revealed attacks of increasing severity in which, on exposure to cold, all of the fingers and toes first became white and cold, then blue, and finally red and warm. After many years, these symptoms became more pronounced, and the skin of the hands, arms, thorax, and face began to lose its flexibility, resulting in retarded motion. Exposure to cold intensified all symptoms.

General examination was essentially negative except for the changes incident to the scleroderma. There was evident thickening of the skin of the face, the wrinkles being ironed out, and definite limitation of motion on opening the mouth, and protruding the tongue. The skin over the thorax had a definite sheen and could not be rolled under the fingers. The hands appeared waxy, the fingers were stiff and permitted about 25 per cent flexion. The joints of the fingers were enlarged and tender to pressure and the hands were cold and moist.

Because of the evident association of vasomotor spasm and the failure of other types of treatment to control the progress of the disease, sympathetic ganglionectomy was carried out and the stellate and second thoracic ganglia were removed from each side (Fig. 1). As early as the seventh day following operation, a decided change in the facial expression was noted; the normal pink hue had replaced the waxy appearance, and the skin was decidedly softer. There was also a slight increase in skin temperature. The stiffness of the hands began to improve until by the fifteenth day after operation the skin of the fingers up to the first joints was normal in appearance. All the fingers were warm, but the mobility was not increased. The mouth could be opened wider and the tongue protruded farther.

One year and 10 months after operation, the patient returned and her general condition was found to be excellent. There was definite improvement in the scleroderma of the hands, thorax, and face. The hands were warm and, although a little stiff, had shown great improvement.

Slight changes were noted in the ganglia similar to those in the ganglia removed for the lesions mentioned already. Most of the arterioles and small arteries in the ganglia were normal, and in a few there was slight proliferation of the lining endothelial cells of the intima. There was no thickening of the walls of the vessels, and the normal ratio of wall to lumen was constant throughout. There was

no inflammation, acute or chronic, and there was no increase of the connective tissue, although there was a slight amount of œdema, but this was not universal throughout the ganglia. It was present in less than 50 per cent of the cases. Although there was no inflammation there were small collections of lymphocyte-like cells in the ganglia in this case, but in the ganglia from the entire group it was present in only 30 per cent. In the ganglion cells themselves, there was slight chromatolysis in a few, approximately 25 per cent, and in the entire group of ganglia removed from patients suffering from scleroderma, chromatolysis was present to this degree in only 30 per cent. As in ganglia studied from all conditions, there was vacuolization of the periphery of the cytoplasm of the cells and this corresponded to the swollen endocapsular cells. This proliferation corresponded in degree and site to the vacuolization of the cytoplasm of the ganglion cells. Pigmentation was visible in most of the cells, but was usually slight. It was present in the same mild degree in 75 per cent of the ganglia removed for this condition. The average age of the patients in the entire group was 35 years. In the cases in which there was no pigment the average age was 27.5 years; in the group in which pigment was graded 1 the average age was 37 years. Pigment was not graded more than 1 in any case. The finding of pigment in the ganglion cells supports the observations made in ganglia removed for the other conditions, that there is a deposition of pigment with advancing age.

HISTOLOGICAL STUDIES OF NORMAL GANGLIA

The ganglia which we used as control material for this study were obtained at necropsy in 40 consecutive cases in which death had resulted from various causes. None of the patients had suffered from any of the four conditions which we have considered. We sought the same changes that we had looked for in the various conditions mentioned. Less than half the vessels were normal, but the changes which were present were slight, and most of them can be accounted for on the basis of age. The walls of the vessels were slightly thickened in more than 50 per cent of the subjects, and in a few (one-eighth) there was proliferation of the endothelium lining the intima, and as in the vascular conditions, this was slight, much slighter than is constantly seen in cases of severe, or even mild, hypertension. There was no sign of acute or chronic inflammation or increase in the connective tissue in the ganglia, occasionally the connective tissue was much looser in texture and slight œdema was present; this was probably the result of local inflammation which was present in several cases. Lymphocyte-like cells were present in small groups, but less frequently than in any of the other conditions, and this was the only observation which varied from those constantly noted in the ganglia removed in the other cases considered. The ganglion cells themselves showed changes similar in type and degree to those we observed in the other cases. Chromatolysis was present in a few ganglia, and cystic degeneration of several ganglion cells was also seen; swelling of the endocapsular cells which corresponded to the vacuolization of the periphery of the cytoplasm of the ganglion cells was common. The most interesting observation was that of pigment in the ganglion cells. The various ganglia were studied, the changes noted, and the degrees of change recorded without any knowledge of the age of the patient or the condition from which he suffered. The age in the control series was higher than in any other series. The average age in the control series was 46.6 years. More material must be found before definite conclusions can be reached regarding the age at which pigment first appears. The average age of patients whose pigment was graded 1 was 43.7 years; the average age of patients whose pigment was graded 2 was 56.9 years, and the average age of patients whose pigment was graded 3 was 64.7 years. There was, as in any control series, a marked variation in the individual cases, but nevertheless a marked tendency for the pigment to increase with age. This has been our observation for many years, and coincides with that of others.

GENERAL COMMENT

In comparing the histological observations of the sympathetic ganglia, removed for the

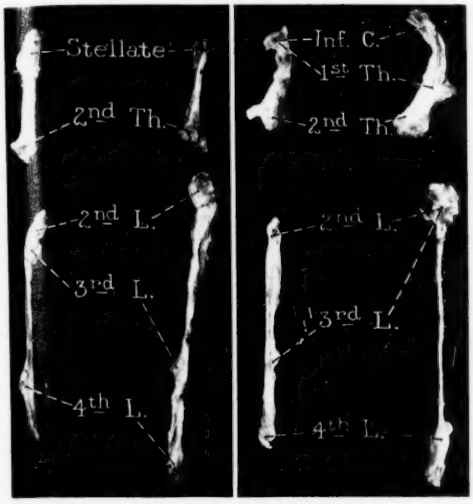

Fig. 1. Cervicothoracic and lumbar sympathetic ganglia removed surgically from cases contained in this series. The lack of uniformity in the anatomical distribution of the ganglia along the sympathetic trunk is well illustrated as well as the tendency for one or more ganglia to be fused.

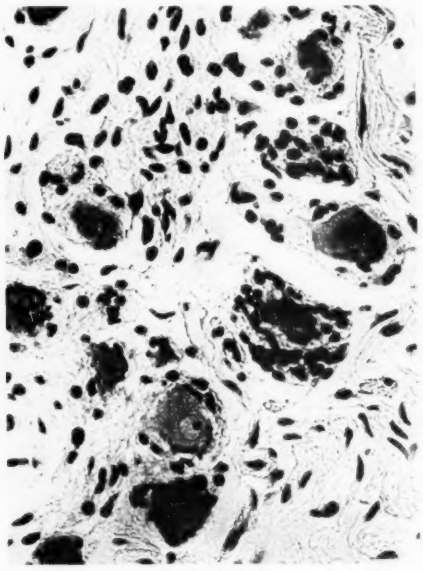

Fig. 2. Marked variation of the degree of endocapsular cell proliferation may be noted. Swelling of some of these cells is present with erosion of their periphery, with the formation of peripheral vacuolization. In one place, the proliferated endocapsular cell has replaced the ganglion cell, and in another only a small remnant of the ganglion cell is seen, and this is pyknotic (toluidin blue ×350).

conditions described, with each other and with those of normal ganglia, nothing was found to explain the various vascular disturbances. All the changes were within normal limits and most of them can be explained on a basis of advancing age. There was no histological difference between the ganglia removed for the various diseases, although these varied much in their clinical manifestations. The blood vessels in the ganglia removed from patients with vascular diseases did not partake of the changes in the blood vessels of the diseased extremities and were similar in most respects to the control vessels. Small collections of lymphocyte-like cells were present in all the ganglia as well as in the control ganglia. These cells closely simulated lymphocytes and differential stains were of little positive value, yet it is possible that they represented proliferated endocapsular cells replacing degenerated or disintegrated ganglion cells. In opposition to this possibility is the fact that they were not always enclosed in the capsule which normally surrounds ganglion cells, although endocapsular cells surround the dendritic processes of the ganglion cells. These cells were always in groups and not scattered diffusely throughout the ganglia. They were not associated with blood vessels, which is frequently the case in inflammation of the central nervous system. Sympathetic ganglion cells are surrounded by a delicate capsule, which is covered on the outside by a layer of flattened elongated cells of connective tissue origin and are referred to as ectocapsular cells, whereas the inner side of the capsule is lined with a layer of cells which we have referred to as endocapsular cells and to which von Lenhossek gave the name "amphicytes" and Cajal called "satellite cells." The origin of these endocapsular cells is not yet definitely established, but we think that they are analogous to oligodendroglia, just as De Castro considers the analogous cells of the ganglia of the spinal nerves a type of neuroglia similar to Hortega's oligodendroglia, rather than of mesodermal origin. In this way they simulate the satellite

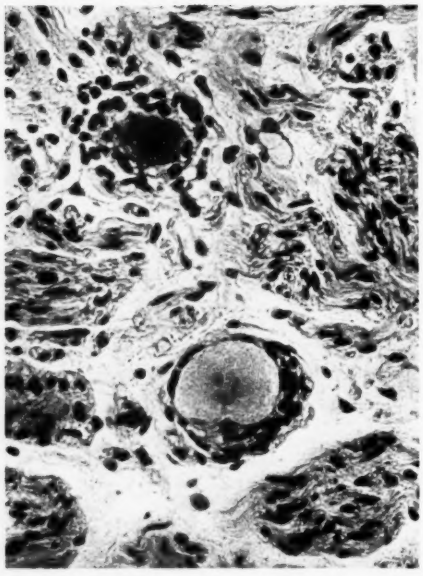

Fig. 3. Endocapsular cell proliferation in one cell, with vacuolization of the periphery of the cell. In another cell, ectocapsular cell proliferation is demonstrated. These cells are flattened (hæmatoxylin and eosin ×335).

cells of the central nervous system. Their reaction, both in the normal ganglia and in those surgically removed, is similar to the acute swelling of the oligodendroglia described by Penfield and Cone, and which have been shown to be analogous to the mucocytes of Grynfeltt. The swollen endocapsular cells of the sympathetic ganglia were surrounded by clear spaces similar to oligodendroglial cells. It is with the greatest difficulty that cell bodies belonging to these cells could be demonstrated, even with Hortega's silver carbonate method. Cajal's gold chloride and sublimate method also failed to reveal cell bodies. None of the swollen endocapsular cells contained débris which had an affinity for silver indicative of phagocytic activities, so that the indentations in the ganglion cells were not the result of phagocytosis. However, mucus stains showed that some, at least, of the spaces around the endocapsular cells contained a slight amount of thin mucus. This was not constantly present, but was seen with sufficient frequency to produce a similarity to the mucocytes, which Bailey and Schaltenbrand have shown to be acutely swollen oligodendroglial cells. In only a few ganglia these endocapsular cells appeared to be proliferated (Fig. 2). Even more rarely were the ectocapsular cells proliferated, although in the few instances in which it had occurred it was quite definite (Fig. 3). Most of the large cysts which caused compression and frequently complete destruction of the ganglion cells contained abundant and easily demonstrable mucus. Some of the sympathetic ganglion cells had a ragged appearance (Figs. 4 and 5); this we have referred to as vacuolization considered to be the result of the acute swelling of the endocapsular cells which occasionally contain mucus. This process may become quite pronounced, and the vacuolization may produce marked reduction in the size of the cell body, simulating the corroded cells of the spinal ganglia, which have been described by De Castro (Figs. 4 and 5). In none of the ganglia which we have studied had it progressed to the degree described by De Castro, or led to complete disintegration of the ganglion cell. Around most ganglion cells in fixed preparations there is a definite clear space separating it from the cell capsule. This space varies much in different cells, and it appears to us to be an artefact due to shrinkage of the cell during the process of fixation. The presence of pigment granules in the cells of the sympathetic ganglion is recognized by all investigators, and it increases with age so that in elderly persons most cells contain numerous pigment granules. Our study of the sympathetic ganglion cells confirmed the observations of others that the pigment increases with age and that it is made up of two types, the lipochrome, or fat-containing pigment which stains with sudan III, and the fat-free type which has an affinity for silver, and is probably a true melanin pigment. Increase in the deposition of pigment in the body during the later decades of life is not limited to ganglion cells of the sympathetic nervous system, but it increases in the ganglion cells of the central nervous system, and in many other organs. In our study of the ganglion cells of the sympathetic nervous system, a definite increase with advancing age

Fig. 4. A group of four ganglion cells, one of which is normal; one shows the effect of the capsular cell proliferation with the vacuolization of the cell body (silver impregnation ×700).

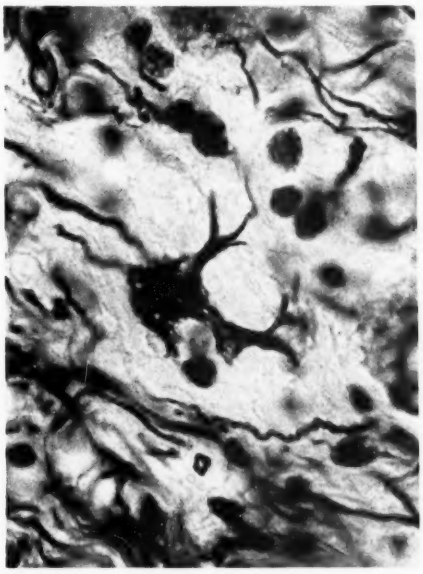

Fig. 5. This ganglion cell shows one large vacuole encroaching on its cell body. The nucleus of the swollen endocapsular cell, which caused the vacuole, is visible (silver impregnation ×840).

was constantly noted, and we feel that this has no connection with the disease process for which the ganglia were removed. Occasionally many bright eosin staining granules are intermingled with the pigment granules. The significance of these eosinophilic granules is not clear. With silver impregnation methods the outline of most ganglion cells appeared normal with their numerous processes extending in all directions into the surrounding tissue, and neurofibrils appeared normal (Figs. 4 and 5). Occasionally ganglion cells were compressed by cysts which we have noted in consideration of the various cases, and even the remnants of the compressed cells had a strong affinity for silver nitrate (Figs. 4 and 5). The same silver impregnation methods demonstrated the fact that axis cylinders were present in normal numbers, and they seemed to be normal in outline and regular in their course and distribution.

These various observations lend support to the conclusion, which has frequently been advanced, that the noxious agent causing the vascular diseases, for which operative relief has been instituted, does not act on the sympathetic ganglia removed. Since the removal of the sympathetic ganglia leads to improvement of the blood supply to the affected limbs it would seem that the ganglia act simply as relay stations for impulses from higher centers, where the disease originates.

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STUDIES ON BRONCHIAL OCCLUSION BY THE METHOD OF ADAMS AND LIVINGSTONE[1]

ALFRED BLALOCK, M.D., AND W. M. RAYMOND, M.D., NASHVILLE, TENNESSEE

THE absence of a safe and satisfactory method of occluding large bronchi has been a great handicap to the development of surgery of the lungs. The recent important experimental work of Adams and Livingstone, in which bronchi were occluded by the local application of a 35 per cent solution of silver nitrate, has possibly supplied a method which may be of vast benefit in the treatment of patients with pulmonary disease.

In attempting to repeat the work of Adams and Livingstone (2), in order to satisfy our own curiosity, several difficulties were encountered that are being reported in this paper. In addition, studies were performed under several experimental conditions that have not been investigated by them.

Dogs and cats were employed as the experimental animals. A 35 per cent solution of silver nitrate was used in all experiments. A small piece of cotton that had been placed on a bronchoscopic forcep was saturated with the silver nitrate and the application to the bronchus was made through a bronchoscope. Morphine was used as the anæsthetic for the dogs and nembutal for the cats. Ether anæsthesia unaccompanied by the injection of atropine was tried in some of the experiments but there was such a profuse secretion into the bronchus that the silver nitrate did not exert its effect.

Cats were used as well as dogs because the mediastinum of the cat is more rigid than that of the dog. Attempts were made to use rabbits which have a still more rigid mediastinum but due to the small size of the trachea, these attempts were abandoned. In the first group of experiments on both dogs and cats, the death rate was high. Seven of the first 10 dogs died and 8 of the first 10 cats lived only a short while. Death frequently occurred within 48 hours following the application of the silver nitrate and it was usually associated with hæmorrhage. The animals which died several days following the application showed at autopsy a pneumonic consolidation of the lobe the bronchus of which had been cauterized. A similar appearance was noted in one dog that lived 15 days. In one dog that was killed 55 days following the application of the silver nitrate, there were several rather hard areas in the lobe in question, the neighboring bronchi were dilated and contained mucoid material. The rest of the lobe was air containing. In a cat that died 26 days after the application, part of the lobe the bronchus of which had been cauterized was completely atelectatic while the remainder showed a pneumonic consolidation. In several of the animals one or more of the lobes were completely atelectatic as has been described by Adams and Livingstone. A photograph of the lungs of a cat which shows complete atelectasis of the left side is given in Figure 1. This animal was killed 27 days following the application of the silver nitrate.

The mortality rate has been very much lower in our subsequent experiments and we believe that the high rate in the earlier studies was due partially to the fact that we did not rid the cotton pledgets of the excess of silver nitrate. It seems likely that the pressure of the pledget against the bronchus squeezed some of the solution out of the cotton and allowed it to escape into the smaller bronchi.

Embolic lung abscesses were produced in 10 dogs by the method described by Holman, Weidlein, and Schlueter. Two weeks later a 35 per cent solution of silver nitrate was applied to the bronchus of the affected lobe. Three of the dogs died several days following the application. The 7 remaining dogs were subjected to autopsy 6 weeks later. A residual abscess was found in 4 of the 7 dogs. The bronchus of the diseased lung was not occluded in any of the 7 dogs. In 2 animals in which the abscess was in the right lower lobe, the bronchus of the right accessory lobe was found to be occluded and the lobe was completely atelectatic while the bronchus of the diseased

[1] From the Department of Surgery of Vanderbilt University.

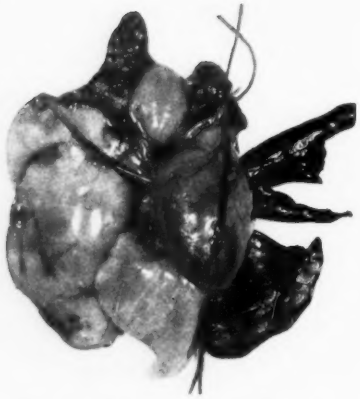

Fig. 1. Heart and lungs of a cat showing complete atelectasis of left lung following the application of silver nitrate to the bronchus.

Fig. 2. Showing complete atelectasis of right accessory lobe. The right lower lobe is air containing and a small residual abscess is to be seen.

lobe was not occluded and the lobe was not atelectatic. A small residual abscess was present in the lower lobe in these 2 instances. The accompanying photograph (Fig. 2) shows the atelectatic accessory lobe and the non-collapsed right lower lobe of one of the dogs. A small abscess can be seen in the right lower lobe.

Adams (1) has recently found that the application of silver nitrate to the bronchus of a lobe containing an experimentally produced pyogenic abscess usually causes delay in the healing of the abscess. Our findings in this respect are confirmatory of his.

Intrapulmonary disease in the human is frequently associated with thickening and stabilization of the mediastinum, or adhesions between the visceral and parietal layers of pleura, or both. The condition of affairs in the chest of the normal dog is quite different and particularly so since the dog has an extremely thin and easily movable mediastinum. In order to try to render the chest of the diseased human and that of the dog more nearly comparable, two types of procedures were performed. In 5 dogs, a portion of one of the lower ribs was removed and the right lower lobe was sutured in a number of places to the chest wall and the visceral pleura of the lobe was painted with mercurochrome. Two of the dogs died of empyema. After the incisions had healed in the remaining dogs, silver nitrate was applied to the region of the right lower lobe bronchus. Six weeks later the animals were killed. There were fairly firm adhesions between the right lower lobe and the chest wall. The bronchus to the right lower lobe was not occluded. In one of the animals, the bronchus to the right accessory lobe was occluded and the lobe was atelectatic. In experiments on 4 dogs, an intercostal incision was made on the right side and the mediastinal pleura was painted with 3.5 per cent iodine. Two of the animals died of empyema. After the incisions had healed, silver nitrate was applied to the right lower lobe bronchus. The two animals were sacrificed and autopsied 6 weeks later. The mediastinum of each was thickened but was not absolutely fixed. There was no bronchial occlusion in either of the animals. We do not believe that these experiments are highly significant because the number of animals is small and because repeated applications of the silver nitrate would probably have resulted in occlusion.

Attempts were made to produce bronchial occlusion in puppies approximately 6 weeks old for the purpose of studying the alterations in the lungs after the dogs reached the full development. The mortality rate in these experiments has been very high. Most of the animals had severe paroxysms of coughing.

Several of the puppies lived less than a week following the application of the silver nitrate. Death of 3 of the animals occurred 4 weeks, 5 weeks, and 6 weeks following the application of the silver nitrate. Clear fluid was present in both pleural cavities of 2 of these. There was complete atelectasis of the left lower lobe of one of the puppies while the 2 remaining showed a pneumonic consolidation without bronchial occlusion.

The output of the heart and the maximum and minimum blood pressure were determined in experiments on 3 dogs before and after the production of atelectasis of the left lower and the right accessory lobes. No significant alterations in either the cardiac output or the blood pressure were found. The occlusion of a greater number of bronchi would probably be associated with changes in the cardiac output and blood pressure.

SUMMARY

The method of Adams and Livingstone of producing bronchial occlusion by the local application of 35 per cent silver nitrate has been employed in experiments on dogs, puppies, and cats. The extremely high death rate in the early experiments was probably due partially to the use of an excess of the silver nitrate solution. The dangers were lessened but not entirely eliminated by observing this precaution. When the attempts at bronchial occlusion were successful, the alterations in the bronchus and in the atelectatic lobe of the cats and puppies were similar to those that have been described by Adams and Livingstone for the dog.

Attempts at occlusion of the bronchus of a lobe that contained an embolic pyogenic abscess were unsuccessful. The abscess did not alter the ability of the silver nitrate to close the bronchus of an adjacent lobe. In the several experiments in which adhesions between the visceral and parietal layers of pleura had been produced and in those in which a thickening of the mediastinum had been caused by irritants, the single application of silver nitrate did not result in an occlusion of the bronchus. The occlusion of the left lower and the right accessory lobes of dogs did not cause significant alterations in the cardiac output and blood pressure.

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CLINICAL SURGERY

FROM THE GRAND RAPIDS (MICHIGAN) CLINIC

SURGICAL MANAGEMENT OF LIP MALIGNANCIES

FERRIS SMITH, A.B., M.D., F.A.C.S., GRAND RAPIDS, MICHIGAN

THE initial small malignant lesions about the lips are simply and effectively managed either surgically or by some other destructive agent. The larger, more advanced lesions, which do not require destruction of more than one-third of the lip may be removed and the lip repaired without the introduction of foreign tissue.

Lesions requiring destruction of more than one-third and, possibly, the total lip, have been less boldly and, frequently, badly managed because the attendant had no satisfactory technique for a repair of the surgical defect.

Few, if any, of the operations described in texts for large partial or total lip reconstruction should ever be employed. Practically all of these operations contemplate the use of full thickness cheek flaps which are cut without regard for the muscles of expression about the mouth, or for blood and nerve supply. The included muscle atrophies in most instances and supplies only a scar filling which is without function.[1]

Methods of reconstruction should be limited to those that conserve all function remaining after the lip destruction; frequently it is possible to restore the major function in the repaired part. It is never necessary to cut into the musculature about the defect. An entire upper or lower lip may be lined and covered from the vicinity of the defect with a minimum of visible scar. The cosmetic result under such circumstances will, obviously, approach as near the normal as is possible in any surface repair.

Confidence, born of the certainty of such restoration, will permit both the patient and the physician to attack the problem boldly, and with greater hope of a successful solution.

SMALL LESIONS

The amount of tissue removed is determined by the size and character of the lesion. The lines of excision should be slightly curved so that approximation will result in a small elevation of the lip border at the line of suture. This elevation prevents the formation of a notch in the lip border as the result of linear scar contraction.

[1]Ferris Smith, Nelson's Reconstructive Surgery.

LARGE LESION WITH AND WITHOUT METASTASIS

The management of these lesions is completed in 3 stages: first, destruction of the lip lesion with or without block dissection of the neck; second, reconstruction of the lip; third, cosmetic corrections.

The first stage, requiring block dissection, is performed under general anæsthesia, utilizing either avertin or ether vapor. Those cases requiring only dissection of the submental and digastric triangles are operated upon under local anæsthesia, supplemented with sodium amytal or nembutal.

The lines of skin incision should be placed at least 1 centimeter on either side of the palpable borders of the lesion. These incisions are carried from the free margin of the lip to the buccal sulcus or as far beyond as the lesion requires. In those cases in which the lesion involves only the lip, the excision is completed by carrying a horizontal incision along the sulcus about 3 to 5 millimeters from the fornix.

The management of the borders of this excision must anticipate the reconstruction of the lip. To accomplish this, flaps for a lining to replace the excised mucosa, for the outer skin covering and for the vermilion free margin, must be so planned that ample material enjoying an adequate blood supply is available.

The blood supply of the lining flap, which will be reflected from the skin adjacent to the angle of the mouth, must come from the buccal mucosa and the muscle bordering the incision. Consequently, the mucosa on this edge must be undermined and accurately approximated to the skin with fine, closely placed horsehair sutures. This produces a minimum of scar and a maximum blood supply. This blood supply is usually

Fig. 1A.

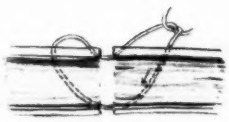


Fig. 1B.

Fig. 2.

Fig. 1A. Vertical mattress sutures of horsehair or ophthalmic silkworm gut are passed through the mucosa and muscle beneath the skin and are tied on the mucous surface of the lip. These sutures provide both approximation and relaxation.

Fig. 1B. Detail of stitch.

Fig. 2. The skin is closed with horsehair which is replaced on the second day with gauze collodion strips to prevent stitch scarring. These supports should remain in place for ten days.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 3. Stage 1.

Fig. 4. Stage 2.

Fig. 5. The posterior margin of the mucosal flap is sutured with horsehair to the free margin of the reflected lining flap and also to the mucosa in the angle of the mouth.

adequate but it can be guaranteed by outlining, partially undercutting, and reapproximating this skin flap at this stage (*A*, Fig. 3).

The mucosa bordering the edge of the lip remnant is similarly undercut and sutured. This mucosa will be utilized to form the free vermilion border of the reconstructed portion of the lip (*C*, Fig. 4).

The skin bordering the excision—chin or face and nose in the case of a lower or upper lip—is undercut and accurately approximated to the mucosal remnant along the buccal sulcus.

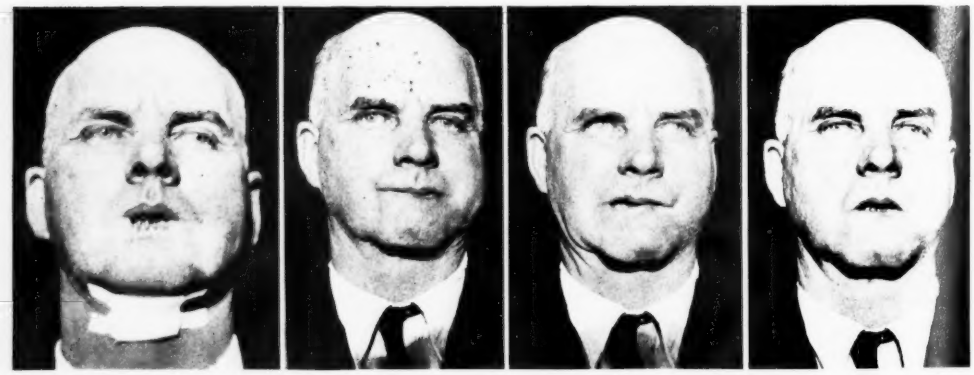
These suture lines are painted with compound tincture of benzoin until they are thoroughly sealed. A strip of gauze is fastened with collodion to the cheeks on either side to limit movement. No other dressing is applied.

The flaps for the lining, *A*, and the covering, *B*, are outlined. They may be raised and sutured in their original locations at this time if the blood supply is questionable. The blood supply, however, is usually excellent.

The mucous membrane on the incised edge of the lip remnant is removed between two parallel incisions placed 1 centimeter apart. One incision is carried down its union with the skin and the other through the mucosa on the posterior surface of the lip. Its blood supply is formed by the mucosa on the free margin of the lip and a broad portion of mucosa posteriorly. This flap, *C*, held

A. B. C.

Fig. 6 A, Perforating carcinoma creating a pathological harelip. B, Appearance of the lip 2 weeks after excision. The removal of the lesion included the tissue bordering the nasal ala. The defect has been closed by loosening the cheek tissues from the underlying bone and suturing to the base of the nose. C, Appearance of the lip 6 years after operation.



A. B. C. D.

Fig. 7. Carcinoma of the mid-portion of the lower lip. A, Appearance 2 weeks after excision of the lip and dissection of both digastric and submental triangles. D, The reconstructed lip. B and C, Demonstration of the muscular action which is now possible in the reconstructed mouth.

on the sharp hook, will form the vermilion border of the reconstructed lip.

The skin flap, (*A*, Fig. 3) carrying underlying fat, is turned from the face on a "hinge" and sutured to the incised margin of the mucosa on the posterior surface of the lip remnant.

The covering flap (*B*, Fig. 3) is incised and elevated with the underlying fat.

The skin of the face on either side of the defect resulting from elevation of the covering flap (*B*, Fig. 3) is freely undercut and approximated with horsehair sutures. The approximation of these skin edges adds two-thirds of the width of the flap to its length.

The covering flap (*B*, Fig. 3) is rotated 90 degrees to cover the lip and the defect left by reflection of the lining flap (*A*, Fig. 3). The opposing skin edges are sutured with horsehair.

The anterior edge of the mucosal flap (*C*, Fig. 4) is sutured to the free edge of the covering flap with horsehair.

The teat, (*D*, Fig. 5) created by the rotation of the covering flap (*B*, Fig. 3) is adjusted by the removal of excess skin and suture. This should not be done sooner than the twelfth day because of possible damage to the adequate blood supply of the transplanted flap prior to this time. Any other cosmetic defects are corrected at this period.

The suture lines about the mouth are painted with compound tincture of benzoin and those on the face and neck covered with a gauze dressing wet with alcohol.

All skin stitches are replaced on the second or third day with gauze collodion supports which are maintained a minimum of 10 days.

The lining of the lip which is formed by reflection of the skin from the face is annoying to male patients because of the growth of hair. This can be replaced after 60 days with normal mucous membrane from the cheeks. The repair is effected by multiple excision. Approximately one-half the skin can be removed at the first stage and buccal mucosa advanced to fill the defect. Sufficient relaxation of the mucous membrane will again occur at the end of 4 to 6 weeks to permit the excision of the remaining skin.

It is sometimes advisable to utilize flaps from both sides of the mouth in the construction of an entire lip. When this method is followed, a long covering flap and shorter lining flap should be cut on one side and the reverse procedure practised on the opposite side. This will place the junction line of the covering flaps at a different point than the union of the lining flaps and prevent a depressed, adherent scar line.

This plan of management permits the boldest attack on the local lesion and, at the same time, provides a method of repair which is highly satisfactory from both functional and cosmetic standpoints.

FROM THE KASR EL-AINY HOSPITAL, CAIRO

A TECHNIQUE OF TUBO-UTERINE ANASTOMOSIS (IMPLANTATION) IN INTERSTITIAL AND ISTHMIC OCCLUSION

AHMAD SHAFEEK, M.B., B.S. (LOND.), F.R.C.S. (ENG.), CAIRO, EGYPT
Gynecological and Obstetric Surgeon to Kasr El-Ainy Hospital

TUBAL implantation, if it should at all serve the object for which it is done, must be planned so as to give the utmost uterine security both during pregnancy and labor. It should not disturb the normal anatomy by injuring the musculature of the uterus or its cornual sphincters.

It should as well aim at conserving the salpingo-uterine continuity permanently. Mere implantation into the uterine cornua and the bringing together of uterine and tubal mucosa (end-to-end union) is insufficient. Even if permanent permeability is thereby attained, the line of junction might become constricted, which would defeat our object.

INDICATIONS AND CONTRA-INDICATIONS

The choice of cases for implantation cannot usually be definitely decided beforehand, as we cannot foretell whether or not sufficient tubal length will be available. It is therefore clear that abdominal exploration is necessary; even if tubal implantation is not found feasible, we would then be able to liberate adhesions, resect any diseased part of the ovary or the tube, or correct the uterine position, if any of these conditions is present.

Tubal implantation is indicated under the following circumstances:

1. In the presence of sterility with interstitial blockage that shows no evidence of any actual adnexal inflammation.

2. Or in cases in which there had previously been adnexal inflammation which had been relieved and there had been no recurrence for a sufficiently long period, i.e. about a year's time.

Pre-operative hysterosalpingography should always be done, preferably not less than a week beforehand. A course of treatment with tampons and douches is done afterward to alleviate any irritation caused by the manipulations or the lipiodol. Implantation would naturally have no place in cases that show definite uterine infantilism or atrophy, or in cases of ovarian hypofunction whether primary or secondary to the chronic pelvic inflammation and adhesions. Restitution of anatomical and functional permeability fulfills no object in such cases.

STEPS OF THE OPERATION

The usual vaginal toilet is carried out.

The cervix is dilated to the size of a No. 8 Hegar dilator so that a Bonney insufflator can be inserted without any leakage. The insufflator is left *in situ*.

Abdominal operation. The adhesions are liberated. The uterus and adnexa are delivered through the wound. A sound with a bulbous end is introduced into the abdominal opening of both tubes to determine the extent of their patency and to obtain a clue as to where we should cut the tube across—that is at its innermost permeable point (Fig. 2). We should require at least 6 centimeters of fallopian tube (ampullary and isthmial) for efficient utilization.

The isthmial tube, which is the part usually blocked, is liberated from its mesosalpinx up to the cornu where it merges into the short interstitial part (Fig. 3). At this junction, and with a conscious preservation of the cornu in its entirety, a circular incision through serosa and muscularis is made, until we encounter the fibrosed impermeable core that remains of the interstitial mucosa. This core, with its continuation in the interstitial tissue is patiently and gently dissected

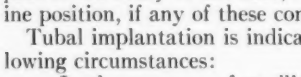


Fig. 1.

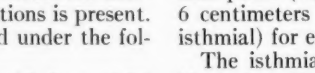


Fig. 2.

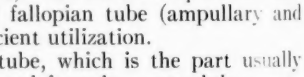


Fig. 3.

Fig. 1. Drawing showing occluded area in tube.
Fig. 2. Drawing showing the innermost permeable point.
Fig. 3. The isthmial tube is liberated from its mesosalpinx up to the cornu.

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 7.

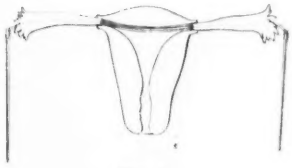


Fig. 8.

Fig. 9.

Fig. 4. Careful dissection enables us to conserve the muscular integrity of the cornua.

Fig. 5. Fenton dilator inserted in both tracts at same time.

Fig. 6. Two catgut sutures have been passed through the whole thickness of the inner ends of the cut tube.

Fig. 7. The suture is being carried out through cornu, uterine fundus, the other cornu, to opposite tube, and out through abdominal incision.

Fig. 8. The sutures have been pulled through in opposite directions so that the inner part of each cut tube is telescoped entirely into the respective cornu to the degree required.

Fig. 9. Later step in procedure.

out from the cornual musculature with a fine knife. If it cuts through, as frequently happens, the whitish spot that represents its continuity serves for further dissection until we open into the cone of endometrium that lines the uterine angle. The dissection is made much easier by the utilization of the Bonney or other insufflator to distend the uterine cavity and thus to bring the endometrial apex of the cornu farther out. The opposite side is treated in a similar manner, and a small dilator is inserted in the opening already made when the insufflator is again manipulated. By this patient dissection we are able to conserve the muscular integrity of the cornua (Fig. 4).

The fine tracts left are then gradually sufficiently dilated by means of the Fenton dilators, the dilators passing through both ends at the same time to admit the passage of a whole thickness of the tube (Fig. 5). Two catgut sutures are passed through the whole thickness of the inner ends of the cut tubes, on both sides, and are tied (Fig. 6). The sutures are then passed through the eyes of two rather long probes which are guided, in opposite directions, through cornu, uterine fundus, the other cornu, to the opposite tube, and out of the abdominal ostium together with the sutures, which are delivered out of the same tract (Fig. 7). The sutures are then pulled upon in opposite directions with the result that the inner part of each cut tube is telescoped entirely into the respective cornu to the degree required (Figs. 8 and 9).

In cases in which the tube on one side is found to be totally disorganized or its patent part so short as not to be utilizable, the sutures placed on the cut end of the other effective tube are made to pass on a needle through the cornual hole and pierce from within outward the corresponding walls of the fundus about its middle line (Fig. 10). These sutures are pulled upon sufficiently to telescope the required length of whole tube inside the cornu.

Interrupted seromuscular sutures are inserted to unite cornu to tubal wall and thus firmly anchor it in position.

Tubo-uterine continuity is thus assured by these steps, and a sufficient amount of the entire tube is invaginated into uterine cornu. The transuterine and tubal lengths of catgut, left *in situ*, further help to secure the permanency of this continuity as they remain there for some 40 days. Sterile oil, or homenol if available, is put in to prevent adhesions. After the operation, the uterus is usually in a good position, and the posi-

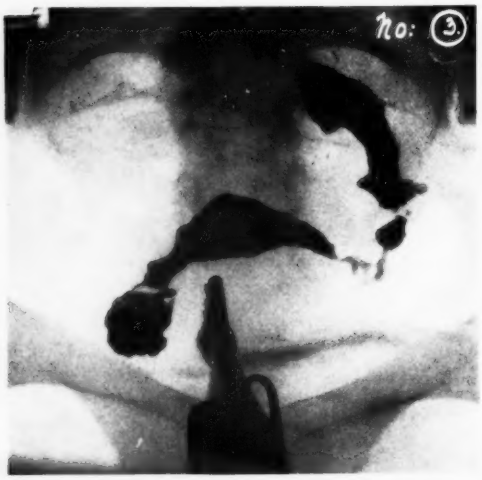
Fig. 10. Technique in case one tube alone is available for implantation.

Fig. 11. Hystero-salpingogram No. 1 showing the blockage of the tubes at both uterine ends. (Private case).

Fig. 12. Hystero-salpingogram No. 2 of same case showing patency of both tubes, after the implantation operation and the passage of lipiodol as oil droplets. Three cubic centimeters of oil only were injected.

tion is insured by the shortening of the mesosalpinx. The permeability could be tested at the time, by the Bonney insufflator which has been left in its original position.

Postoperative hysterosalpingography. Tests are made on repeated occasions, at first 2 to 3 weeks after operation and later on as opportunity arises. In some such patients it was found that the tubouterine permeability was still present even as late as a year and a half after operation.



Figs. 13 and 14. Hystero-salpingograms showing patency of both tubes after implantation. (Hospital cas

ADVANTAGES

The advantages of this operation, which we have been doing for the last 3 years at Kasr El-Aini, lie, primarily, in the maintenance of the muscular integrity of the uterus. The object of the operation is to reinstate tubo-uterine permeability in an effort to overcome this cause of sterility. And it is our belief that a uterus treated as we have described, with the musculature left intact, is better fitted to stand the strain of pregnancy and labor than is a uterus in which the cornua have been incised, cored-out, or resected.

The advantage of the special way by which the tube is implanted in order to secure permanent continuity in its normal direction is evident.

There are two theoretical drawbacks to methods of operation in which the tube is not implanted in its natural site, namely: (1) the fertilized ovum is then implanted lower, and (2) during periods of muscular atony the menstrual fluid may easily be regurgitated and this might lead to the occurrence of pelvic endometriomata.

The appended hysterosalpingograms demonstrate the integrity of the musculature of the cornua of the uterus. They were taken immediately after the injection of the lipiodol, while screening. The conformity of the uterine cornua with the normal shape is well seen.

My thanks are due to Prof. R. S. Dobbin for encouraging me to make this study and for allowing me to use the French literature in his possession; to my colleague Dr. H. Sobhy, obstetric tutor, who has done the operation himself several times; to Drs. Ahmed Marey and Husein Erfan for the radiograms; and to Mr. Strekalovsky the artist to the Faculty for the execution of the drawings.

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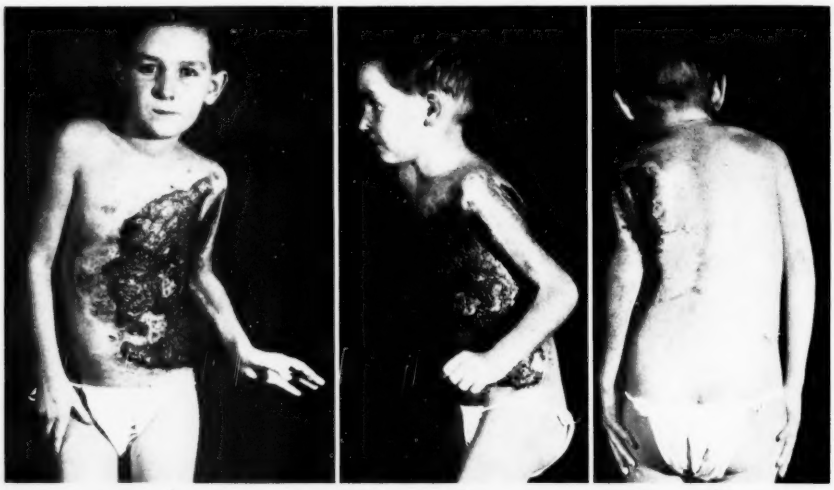
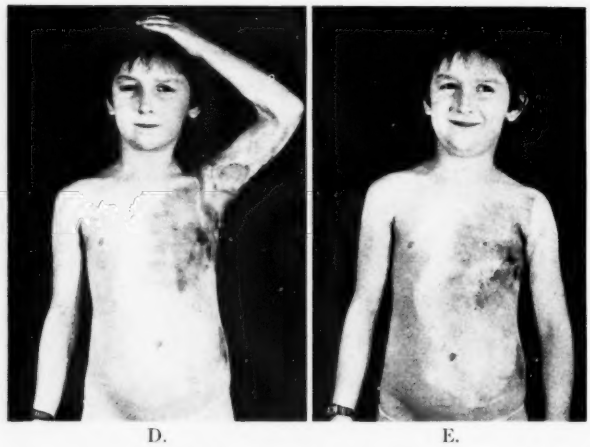


A. B. C.



D. E.

Fig. 1. Prevention of deformity; technique of operation and dressing; after care. A, B, and C, Patient admitted in poor physical and mental condition, with widespread granulating areas from a burn. Surgical cleanliness and firm granulations were obtained by means of salt baths, dry heat, and mild antiseptic (acriflavine) packs. The wounds were kept clean and free of débris; and from scattered islands of epithelium there was spontaneous healing of satisfactory thickness over part of the lower area. D and E, The surface of the entire axilla and much of the chest and arm was restored with thick split grafts. Satisfactory bearing surface, complete release of deformity and normal function resulted. (Two operations.)

(1) The granulations were shaved from the areas down to a very thin scar base, and some of the full thickness of the scar itself was removed so that complete elevation of the arm was possible. The grafts were removed from the thighs with the aid of the suction retractor. They were accurately sewed in place and extra "quilting" sutures were put through the center of them. Multiple stab holes were made through them and all blood clots expressed.

The dressing was (1) 2 layers of 3 per cent xeroform gauze, (2) several layers of plain gauze, (3) soft sea sponges, and (4) accurate fixation and pressure with large gauze rolls and adhesive plaster. The final fixation of the arm was done with a simple "quilted" bed pad (such as is used in any infant's ward); this was held in place with another gauze roll and adhesive plaster. The arm was placed at 90 degrees abduction, and the elbow at 90 degrees flexion, with the arm rotated backward at the shoulder (the "never-again" position). We formerly used plaster-of-paris fixation, but do so only occasionally now, as we have found that this softer fixation is simpler to apply, easier on the patient, and gives adequate support. (See Fig. 9.)

After care. If grafts have been put on an open granulating field, the first dressing is done on the fourth day. (If the area has been clean and healed at the time of operation, the first dressing may be delayed until the sixth or eighth day, unless there is pain, elevation of temperature, or excessive discharge from the wound.) The sutures may usually be removed, and the excess edges trimmed away with sharp scissors. Any pustules, blebs, or blisters are opened and evacuated. If blood has collected under any area, the skin is opened over it, the clot turned out, and the graft allowed to settle back down on the wound. One per cent silver nitrate is gently scrubbed over the edges and any open areas. A wet boric dressing is applied firmly and with the arm fixed in position again with a bed pad. No sea sponges are needed from now on; daily wet dressings are done until the wound is clean enough for a grease dressing, and then they are changed as necessary. As soon as the area permits, active movement is begun. If it is evident that second operations are necessary they are done when the patient is in satisfactory physical condition for further work.

The Release of Axillary and Brachial Scar Fixation.—James Barrett Brown, Vilray Papin Blair and William G. Hamm

THE RELEASE OF AXILLARY AND BRACHIAL SCAR FIXATION[1]

JAMES BARRETT BROWN, M.D., F.A.C.S., VILRAY PAPIN BLAIR, M.D., F.A.C.S.,
WILLIAM G. HAMM, M.D., F.A.C.S., ST. LOUIS, MISSOURI
From the Department of Surgery, Washington University School of Medicine and Shriners' Hospital for Crippled Children, St. Louis

BASED partly upon observations made in the early or late treatment of 35 cases of deep burns about the arm-axilla-chest-region, the following deductions are considered as basic in their care.

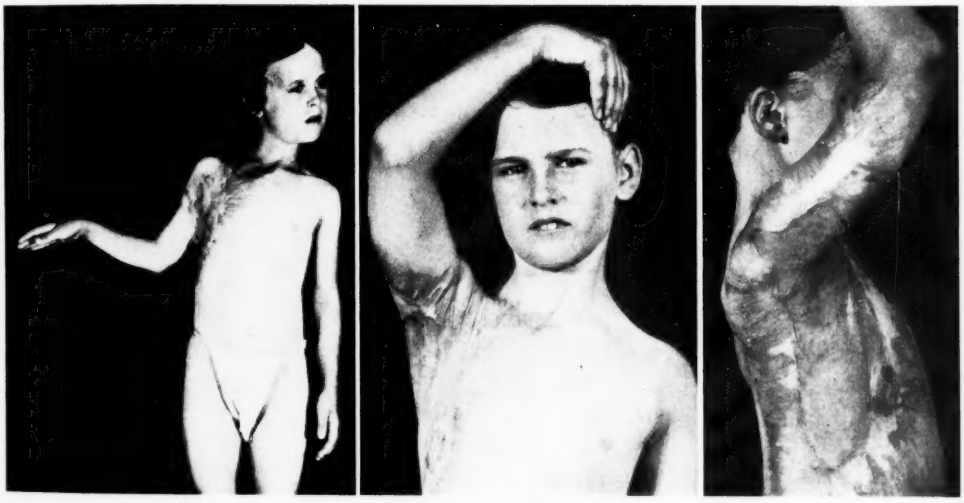
1. In the acute and subacute stages relief of pain, control of sepsis, and maintenance of comfort and the best obtainable general conditions, are of first importance; they may be life-saving and should be established before operative correction is undertaken.

2. Comfortably applied moist hypertonic salt dressings or baths with alternate periods of dry heat are definitely helpful.

3. Traction or fixation to prevent scar contraction will, even when carefully applied, fail in its object and may be detrimental.

4. Early surfacing of areas in which the full thickness of the skin has been destroyed shortens invalidism and prevents or lessens the ultimate disability that would result from scar fixation.

5. Fixation that has occurred can be released by cutting or removing all binding scars, but this mobilization can be made permanent only by



A. B. C.

Fig. 2. Restoration after widespread loss; one operation; method of freeing contracture. A, Complete healing of arm to side 1 year after burn. B and C, The defect resulting from relaxing the scar was extremely large, and no flaps were available for covering the apex. The entire area was covered with split grafts at one operation. Result is a good bearing surface, no remaining scar bands and full range of motion. The grafted area is outlined and it is seen to be so large that any attempt at repair with full thickness grafts or flaps would result in great deformity elsewhere in the body. This patient also had a dislocated cervical vertebra which was presumably sustained at the time of the burn. She was treated for this by Drs. Theodore Brookes and C. H. Crego.

In relaxing this type of contracture, incisions are placed to allow opening of the area with preservation of any flaps possible for covering the apex of the axilla. It is well to have one assistant do nothing but hold the arm and gently extend it as the scar gives way. Tightness of the skin from the deltoid region to below the clavicle and over the posterior aspect of the arm must be opened and the defect grafted. Even a small triangle of opening is important in these areas, and, if the graft is successful, this may make the difference between complete and partial freedom of motion. One of these small important areas is shown in this patient and one in Figure 3.

The necessity of removing any tissue will depend on the surface type of scar and the thickness of the deep scar. In this patient practically no skin or scar was removed. The contracture was opened, the arm gently elevated, and the edges gently dissected back. A very large defect was left which was grafted. If there is such heavy surface keloid or deep scarring that the contracture cannot be overcome otherwise, wide areas of scar tissue may have to be excised.

[1]Presented by Dr. Blair at the Southern Surgical Association, Miami, Florida, December 14, 1932.

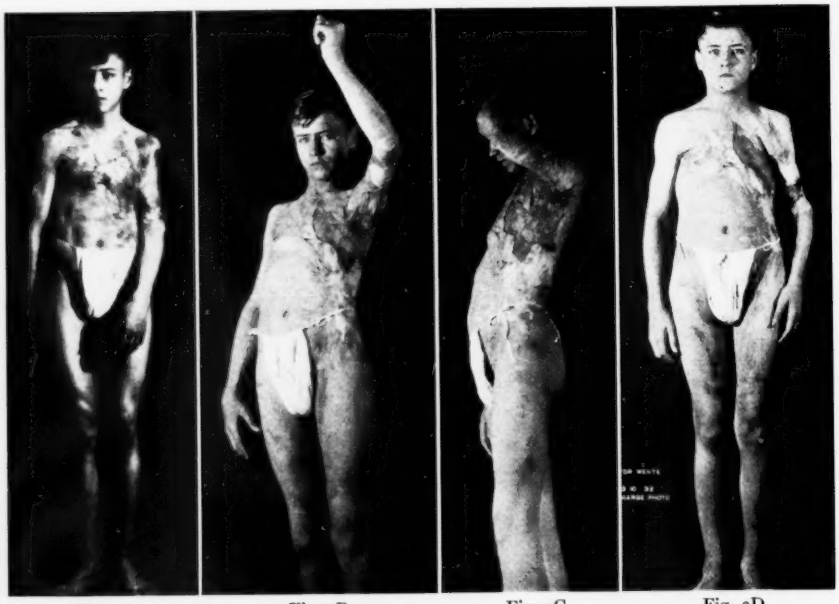


Fig. 3A. Fig. 3B. Fig. 3C. Fig. 3D.

Fig. 4.

Fig. 3. Complete immobilization of arm. Advancement of pectoralis major and latissimus dorsi. Thick split grafts only possible method of covering defect. A, Arm grown solid to body with excessively thick scar over entire side. Deep dirty sinus running high toward axilla, 2½ years after burn. At the first operation the sinus w simply opened and then acriflavine packs were kept o he raw area. At the second operation the contracture w opened widely but the arm would not come up satisfa rily. In consultation with Dr. C. H. Crego it was deci to ad-

Fig. 5A.

Fig. 5B.

Fig. 5C.

vance the pectoralis major and latissimus dorsi upward on the chest wall, and this was done without disturbing the nerve supply and without exposing the contents of the axilla. The muscles were anchored with catgut and the arm could be raised to the vertical. It was necessary to stop the procedure, and the area was dressed with acriflavine gauze. At the third operation (done 48 hours later) the entire area was covered with thick split grafts and the arm fixed with the dressing as described in Figure 1. Accurate measurement of the skin removed from the thigh showed five large areas and one small one, and the total area denuded 173 square inches (1,081 square centimeters). These grafts "took" successfully and good function and free movement up to about 105 degrees abduction were obtained.

At the fourth operation the contracture was opened low across the axilla, and one was opened just above the elbow. The resultant defects were covered with thick split grafts from the thighs. Three denuded areas on the leg measured 48 square inches. Total for both operations of 221 square inches (1,381 square centimeters). The final surface area covered as measured with a paper pattern shows less than one-half this amount. This is not an accurate measurement of field contracture, but rather an index of the large amount of graft one should have to cover one of these areas adequately.

B, C, and D, There is practically complete function, and the power of the pectoralis major and latissimus dorsi has been maintained (see Fig. 4). In D along the posterior edge, note the small triangular insert of graft that allows important relaxation. The thighs show the rather inconspicuous scars of the thick split grafts, and in time another "crop" of grafts can be cut from these same areas to cover the heavily scarred flank if it gives too much discomfort. In B the scars of a few small deep grafts (done before entry to this service) can be seen.

This boy is an ideal type from which to cut thick split grafts by means of the suction retractor. The thighs are large and firm, and not too muscular. In a smaller child with a deformity of comparative size it might be a difficult matter to get adequate grafts for the covering of the defect.

Fig. 4. Physiotherapy. Function. Same patients as shown in Figures 3 and 7 in the gymnasium of the Physiotherapy Department at Shriners' Hospital. It seems that postoperative stiffness and even second contractures in these cases may be easily overcome if a will to help themselves is instilled in the patient and simple equipment is supplied for exercise and play. A trapeze hung in a transom of the hospital or home may suffice. Massage and baking and baths are seldom necessary if the restoration has been adequate and the patient is able to exercise. Function to be complete should, of course, permit complete motion of the arm, but, in some instances, if the arm is gotten to above right angles by one operation, it may be difficult to get the patients to submit to further procedures because they do not feel that they have enough deformity to warrant it.

Fig. 5. Comparison of full thickness and thick split grafts. Breast function and position. A, Arm grown firmly to side, complete destruction of axillary skin, widespread loss on chest, 1 year after burn. B, The deformity was released and the defect covered with a single full thickness graft that included almost the entire lower abdominal skin. C, About 1 year later some limitation of motion remained along the anterior axillary fold. This area was opened, and the defect covered with thick split grafts to give the result shown here taken still a year later. At this time it was impossible to distinguish the full thickness from the thick split graft. The white area is spontaneous healing that has occurred over areas of fairly deep loss. The breast may be elevated out of position, and, if possible, the original operation should correct this by relaxing it and grafting the defect. It may occasionally be pulled down if there has been heavy scarring over the flank and abdomen, and a separate operation and graft may be necessary for elevating it.

If the nipple area has been destroyed and there is heavy scarring over the breast tissue, it is our belief that the gland tissue atrophies and never regains its function. We have never seen any trouble with the breasts whether just heavily scarred or whether the nipple area itself has been destroyed, but pregnancy has not occurred in any patients of this series, and so the observations are not complete.

SUMMARY OF CASES

Type; age in years	Duration of lesion healed or unhealed	Type of graft used	Flap or graft across apex of fossa	Function, areas grafted No. of operations
I 5	6 mos. Healed. Extreme deformity	Full thickness	Graft. No flap available	Both folds, arm, apex. Complete function. One operation
I 5	4 yrs. Healed	Full thickness	Graft. No flap available	Both folds, arm, apex. Complete function. One operation
I 6	1 yr. Healed	Full thickness	Graft. No flap available	Both folds, arm, apex. Complete function. One operation
I 10	14 yrs. Unhealed because of added X-ray burn	Full thickness	Graft. No flap available	Anterior fold, arm and chest to let breast down in place. One operation
I 6	16 mos. Healed	Full thickness	Flap from behind for apex	Both folds, arm, chest. Not complete elevation but only one operation done
I 8	6 mos. Healed. Marked deformity and itching	Full thickness	Graft. No flap available	Both folds, arm, chest, and apex. Complete function. One operation
I 14	6 mos. Widespread keloid and itching	Full thickness and a thick split to cover partial loss of full thickness	Local flap	Abduction gotten from 45 to 105 degrees. Secondary operation refused
I 13	1 yr. Unhealed. Solid growth to side	Full thickness followe l in 1 yr. by a thick split	Graft. No flap available	Both folds, arm, chest, apex. Complete elevat[illegible]. 2 operations
2 13	10 yrs. Healed	Full thickness	Graft. No flap available	Anterior fold and apex. Complete function. One operation for each side
2 38	4 mos. Heavy keloid, intense itching	Full thickness right and left	Neither necessary	Anterior folds and chest. Complete function. 2nd flap operation necessary on left
2 10	5 mos. Marked deformity from a dislocation of the 2nd cervical vertebra sustained at the time of the burn. Neck and axilla unhealed	Thick split	Anterior fold, apex. Breast let down with thick split grafts	Function perfect. One operation, breast dow[illegible] in normal position. Vertebra reduced by Dr. T[illegible]. Brookes
2 6	1 yr. Healed. Had many small deep grafts, with healing but without correction of deformity	Thick split	Local flap	Anterior fold, chest, arm. Two operations. Complete function
2 38	1 mo. Whole chest and right axilla one painful ulcer	Thick split	Neither necessary	Whole anterior chest wall. Anterior fold. 3 operations. Complete function
2 5	2 mos. Unhealed. Very widespread, body, chest, neck, arms	Thick split	Local flaps	Arm, chest, anterior fold. 2 operations. Complete function
3 22	16 yrs. Good webs. Only slight limitation of function. Had 2 operations that only scarred the webs further	Thick split	Local flaps	Chest, anterior fold, arm. One operation. Complete function
3 12	Several yrs. Healed	Thick split	Local flaps	Chest, anterior fold, arm. One operation. Complete function
3 33	6½ yrs. Electric burn. Extreme deformity about elbow but with only a slight web in both axillary folds	No grafts necessary	Local flaps	Anterior fold-apex flap operation. One operation. Complete function
3 13	11 yrs. Deformity both folds, itching and pocketing	No grafts necessary	Local flaps	Both folds and apex flap operation. One operation. Complete function
3 4	1½ yrs. Arm bound to side. Wide scarring	No grafts necessary	Local flaps	Both folds and apex flap operation. One operation. Complete function
3 6	2 yrs. Several operations without relief of deformity	No grafts necessary	Local flaps	Anterior fold-apex flap operation. Comple[illegible] function
1 13	2½ yrs. Arm solid to body with deep dirty pockets. Extremely thick scar over whole side of body	Thick split	Thick split grafts and a scar flap from the chest for ant. fold. No distant flaps available	Both folds, apex, arm, chest, and flank. P[illegible] major and latissimus dorsi taken entire from their origins and advanced toward [illegible]. 2 operations. Over 200 square inches of sk[illegible]. Complete function obtained
1 9	5 yrs. Healed	Thick split	Thick split. No flaps available	Anterior fold, chest, apex, arm. 2 operati[illegible]. Complete function

SUMMARY OF CASES—*Continued*

pe; e in ars	Duration of lesion healed or unhealed	Type of graft used	Flap or graft in axilla	Function, areas grafted No. of operations
1 7	2½ mos. Unhealed	Thick split	Thick split. No flaps available	Anterior fold, arm, apex, chest. One operation. Complete function
1 1	1 mo. Unhealed	Thick split	Thick split. No flaps available	Flank, anterior fold, arm, chest. One operation. Complete function
1 15	1½ yrs.	Thick split	Thick split. No flaps available	Both folds, apex, chest to let breast down flank. One operation. Complete function
1 5	6 mos. Extreme deformity, right and left. Back heavy keloid. Child unable to protect self in falling	Thick split	Thick split grafts. Tried to turn flaps but they were not sufficient	Both folds, apex, arm, chest. Both right and left sides. Three operations. Practically complete function
1 12	2 yrs. Healed. Arm bound to side	Thick split	Thick split grafts. No flaps available	Both folds, arm, chest, apex. One operation. Complete function
1 8	1 yr. Healed. Extreme deformity. Dislocation cervical vertebra at time of burn	Thick split	Thick split grafts. No flaps available	Both folds, arm, chest, apex. One operation. Complete function. Also had reduction of dislocation by Dr. Theo. Brookes
1 10	7 yrs. Still ulcerated in one area. Had 7 operations that did not relieve the deformity and that ruined most of the donor areas for getting grafts	Thick split	Thick split grafts and local flaps	Both folds, apex, arm, chest. Two operations. Complete function
1 7	10 wks. Very widespread severe burn. Cleaned up for operation in a salt bath and with dry heat	Thick split	Thick split grafts. No flaps available	Both folds, apex, chest, flank. 2 operations. Complete function
1 5	9 mos. Heavy scar and painful keloid	Thick split	Local flaps	Grafts arm, both folds, chest. One operation. Complete function
1 7	4 mos. Unhealed. Had one unsuccessful graft elsewhere	Thick split	Local flaps	Grafts, arm, both folds, chest. 3 operations. Complete function
1 11	16 yrs. Electric burn. Extremely heavy scarring, keratosis, and discomfort. Unhealed after 16 yrs. Microscopic diagnosis: squamous cell carcinoma	Thick split	Grafts in apex. Flaps from front and back folded around arm	Grafts, chest, back, arm, both folds, apex. 2 operations. Function almost normal. But result hindered by removal of carcinoma that occurred over flank
1 7	4 mos. Unhealed. Extreme deformity, pain, itching, and contracture	Thick split	Grafts. No flaps available	Grafts, flank, abdomen, both folds, apex, arm. Arm free but repair unfinished
1 4	4 mos. Unhealed	Thick split	Grafts. No flaps available	Arm free but repair unfinished. 2 operations

NOTE.—The term apex is used to designate the uppermost part of the axillary fossa as seen from the outside, and not as the anatomical apex of the inside of the axilla.

The "Type" indicated in Column "One" is for convenience in classification of the deformity.

Type 1. Heavy local scar with binding or direct growth of the arm to the side.

Type 2. Heavy scar or keloid formation over the chest, back or flank, involving one axillary fold and possibly the apex of the axillary fossa.

Type 3. Web formation of one or both folds.

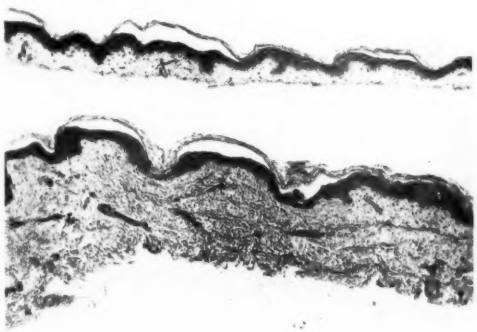


Fig. 6. Thicknesses of skin grafts. Shows relative thickness of Ollier-Thiersch and thick split grafts taken from the inside of a man's thigh. There is a fair thickness of derma attached to the thinner Ollier-Thiersch graft, and we have found that even thin grafts are rarely cut through or above the papillary layer, as is the rather prevalent idea. They are usually cut just below the papillary layer and the bleeding that follows is from the derma rather than from the papilla. The thick, split graft does not look as thick as might be expected. This, however, was cut through a low level of the derma, but the derma itself was not very thick. This graft roughly includes about three-fourths of the thickness of the derma.

The thickness of the derma varies in different parts of the body, on different people, in different ages, and in the two sexes. On the back the epithelium is very thin, but the derma is so thick that the growth of full thickness grafts taken from it is questionable.

Fig. 7A.

Fig. 7B.

Fig. 7C.

Fig. 7D.

Fig. 7. Wide chest, neck, and arm involvement. Local results of and scars of donor area of pinch grafts. A, Complete healing with the aid of pinch grafts one year after burn. There has been wide destruction over the chest, and the breast and nipple are entirely destroyed. The arm is held in by the bridge of scar tissue and grafted surface from the chest. B, This web was opened and no tissue was excised except the ulcerated edge. There was marked immediate retraction of the tissues and the large defect was covered with thick split grafts. A small graft was put in at a second operation when the neck was grafted. Full range of motion has been gotten (see Fig. 4). C, The wide degree of retraction following a simple opening incision is seen by the line of old pinch grafts on the arm, and the line of them far over on the chest. Before operation, as seen in Figure 7A, these grafts were all in the same area over the anterior fold. D, Scars of pinch, or small deep grafts done elsewhere after 1 year's time. Scar of thick split graft after 3 months on inside of right thigh.

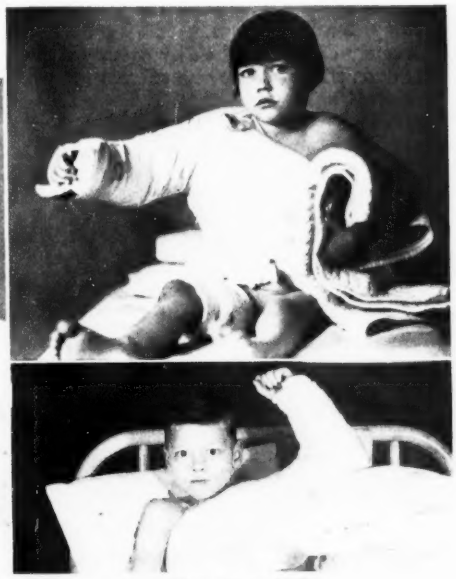
Fig. 8. Utilization of both sides of a web. A, Patient with burn scars of 16 years' duration. The limitation of motion of the arm was not bothering the patient at all, and he sought treatment only because the limitation from the web about the elbow interfered with his work. At operation the axillary web was split in two as outlined, and, without the excision of any surface tissue at all, the retraction of the scarred tissue (which was perfectly soft) was so great that the grafts outlined in C were needed to close the defect. At the same time the web from the arm to the forearm was split and all of it utilized in the closure, but here also it was necessary to use a graft to close the defect, and the graft healed in better than the flaps. Flaps of scar tissue cannot be cut very large or very thin without damaging their vitality. In this case it seemed improbable that grafts would be necessary but on opening the wel there was immediate retraction of the flaps. It is best no to put any tension on these flaps, and this point is emp asized here by the evident looseness of the skin around th elbow in C. In 4 cases out of the series of 35 good enou flaps were gotten so that no grafts were necessary. B Shows relief of contractures in the axillary fold and in th ubital fossa. C, Grafts outlined. Note the different d ree of pigmentation of the grafts—white on chest wh e it is stretched, dark on arm where all surrounding skin lax.

Fig. 8A.

Fig. 8B.

Fig. 8C.

Fig. 9A.



Figs. 9B. and 9C.

Fig. 9. A, Plaster-of-paris cast to support arm. This type of fixation is not necessary and may even be detrimental if there is slipping or twisting of the body inside the cast. B and C, Fixation with a folded bed pad incorporated in the external layers after a firm sea sponge pressure dressing has been applied. This type of fixation is more comfortable, much more easily applied, and with it the patient can sit up without support and be out of bed. It is also much less expensive. The pad is folded in three or four layers and bound firmly on and held with several strips of adhesive. Most of the time the arm should be supported with extra pillows.

surfacing the raw areas, the arm being fixed in abduction.

6. The use of large split skin grafts in sufficient number is a simple and almost universally applicable plan of surfacing these areas.

In the treatment of deep burns about the arm and shoulder, free movement is the ultimate objective and the earlier this can be made the dominant note the better. With the general condition, comfort and morale of the patient all being cared for, the most important step in a recent burn is early complete resurfacing of the denuded area. This will shorten invalidism and lessen, or prevent, further fixation by the scar that occurs with spontaneous healing. (Fig. 1.)

During the period devoted to general preoperative care, the raw areas will contract and partially epithelialize by ingrowth from surrounding skin areas and possibly also from persistent remains of skin glands. Areas that heal from skin remnants may require no further treatment because the full thickness of the derma has not been destroyed, but epithelialization by ingrowth (or seeding) from surrounding skin is for a long time extremely delicate and easily destroyed; and the scar upon which it rests may subsequently have to be shifted or removed to allow free movements.

Even the most severe deformities, including union of the arm to the chest wall, can be relieved by division and dissection that permits the fullest relaxation with complete abduction of the arm. The dissection must be carefully done to avoid injury of the deeper structures, and complete abduction must not involve ruthless rending of underlying muscles. Concurrent grafting is done with the arm held at a right angle to the chest which position is maintained until the healing is completed. (Figs. 2, 3, 9.)

Skin consists essentially of a thick, elastic, deep layer with a thinner, protective covering. Derma normally rests upon a yielding base and epitheliated scar is a very poor substitute for normal skin and subcutaneous tissue; when this scar is thick and unyielding, it is an encumbrance. When lost over a large area, normal skin is best substituted for in most cases with free grafts of split skin of a thickness greater than that of the Ollier-Thiersch graft as it has usually been described. The thick split grafts should be of sufficient size to cover the whole area with one or as few pieces as possible. (Fig. 6.)

When this thick split graft is smoothly fixed to an even firm surface by suture and pressure, it can fulfill the highest possibilities, but when the surface is uneven, a full thickness skin graft may give a better appearance; this point, however, is usually not of importance when the area is covered by the clothes. For a comparison of the technique and uses of the split and the full thickness graft, see references 1 and 2. (Fig. 5.)

Under split grafts there is always some contracture of the base on which they are put, but there is great power in the arm and shoulder actively to resist contraction and, because of this, the split graft is well adapted for covering defects here.

In cases of long standing with the fixation over a limited area, the abductor muscles may have drawn out the scar into one or more soft webs or plicas which permit free movement. In these cases operation is done chiefly to do away with the webbing. The fold is split and each side is converted into an appropriate flap by incisions that may somewhat resemble a "Z." There were 4 such patients in this series. (Fig. 8.)

In 11 of the cases, auxiliary flaps from neighboring skin or soft scar were used in conjunction with split free skin grafts as an extra protection for the axillary vessels and nerves, but, with care, we have so far succeeded in not exposing the axillary contents during the mobilization. In the late healed cases there was usually an increase in the quantity of fat, as happens everywhere that the depth of a natural surface fossa has been lessened by the traction of overlying or neighboring scar.

Treatment of one of these cases is difficult in many ways and well planned surgery of proportionate magnitude will usually prove a saving of both time and effort. On account of the general condition, the scarcity of available skin or for some other reason, pinch grafts, small deep grafts, small Thiersch grafts, implantation grafts, or tunnel grafts might be advantageously used to tide over some phase of the treatment, but these are not always conservative of the donor areas. Homografts might be considered with these mentioned because, at times, they apparently stimulate subsequent spontaneous epithelialization, but in our own cases we have not observed the homograft itself to persist. (Figs. 1, 2, 3, 7.)

Releasing scars and allowing the defect again to contract but adds to the total amount of scar (Fig. 8).

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CANNULA GASTROSTOMY AND ENTEROSTOMY[1]

LESTER R. DRAGSTEDT, PH.D., M.D., H. E. HAYMOND, M.D., AND JAMES C. ELLIS, M.D., CHICAGO
From the Department of Surgery of the University of Chicago

THE production of an artificial opening through the abdominal wall into the stomach or intestine was attempted early in the history of surgery and a great deal of ingenuity has been displayed in the various operative procedures employed. These have been described so thoroughly by R. W. McNealy (1931) that no reference need be made here to this extensive literature. Attention has been directed to the development of simple methods whereby nutrient materials and fluids might be introduced directly into the stomach or intestines at will and yet prevent the escape of the highly irritating digestive secretions which produce such a troublesome excoriation of the surrounding skin. Not only has the operation of gastrostomy and enterostomy been of great service in the clinical treatment, but it has been a most useful tool in the hands of the experimental physiologist in the study of digestion. It is the purpose of the present communication to describe a technique, embodying the principles of one of the older experimental methods with certain modifications, which has been useful to us both in the clinic and in work on lower animals, and which in certain features seems to be an improvement on methods in current use.

Fig. 1. Photograph showing the gold plated cannulas and accessories. Dimensions of the gastrostomy cannula to the left: total length 10 centimeters, inside diameter 1.20 centimeters, diameter of circular flange 4 centimeters. Dimensions of enterostomy cannula at the right: total length 10 centimeters, inside diameter 0.80 centimeters, length of flange 3 centimeters, width of flange 1.5 centimeters.

The essential apparatus consists of a brass tube or cannula with certain accessories all heavily plated with gold throughout. Its shape is best appreciated by inspection of the accompanying photographs and drawings. The cannula with the circular flange is used for the production of a gastric fistula. The curved rectangular flange is designed for the small intestine. The introduction of the cannula is quite simple. An incision is made in the viscus (stomach or intestine) just large enough to admit the flange of the cannula. Closure is made with a running stitch and two purse-string sutures to invert the mucosa snugly about the shaft of the cannula. The greater omentum is now carefully wrapped about the shaft and secured in place by several sutures. This step is most important, since it seals the fistulous tract from the general abdominal cavity and thus prevents a peritonitis. It represents an adaptation of the principle utilized by London (1927) in his

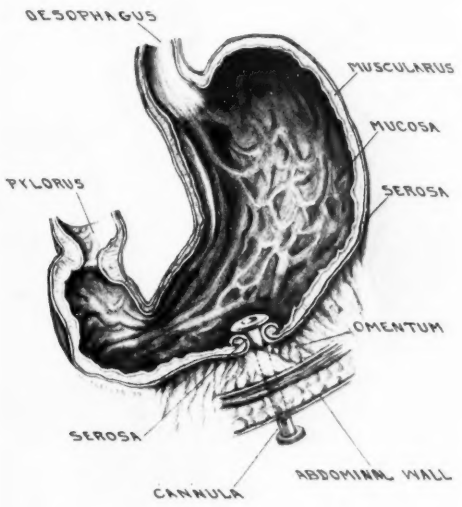

Fig. 2. Drawing illustrating the use of the cannula for gastrostomy. Attention is directed to the layers of omentum interposed between the stomach and the anterior abdominal wall.

[1] This work has been conducted under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

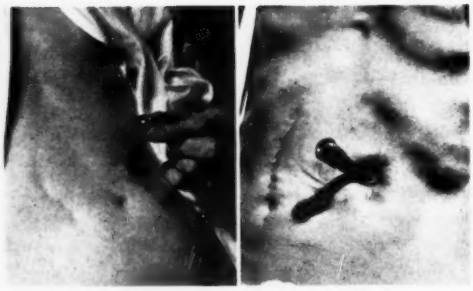

Fig. 3. Fig. 4.

Fig. 3. Patient T. N. Carcinoma of œsophagus. Cannula gastrostomy June 10, 1931. Photograph taken July 15, 1931, about 5 weeks later.

Fig. 4. Patient T. N. Carcinoma of œsophagus. Cannula gastrostomy June 10, 1931. Photograph taken September 19, 1931, about 3 months later.

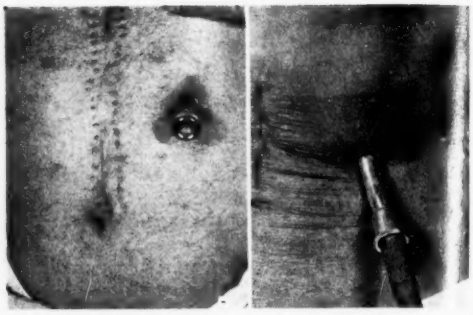

Fig. 5. Fig. 6.

Fig. 5. Patient J. M. Carcinoma of œsophagus. Cannula gastrostomy October 1, 1931. Photograph taken December 5, 1931, about 2 months later.

Fig. 6. Patient S. F. Carcinoma of œsophagus. Cannula gastrostomy January 29, 1932. Photograph taken February 18, 1932, about 3 weeks later.

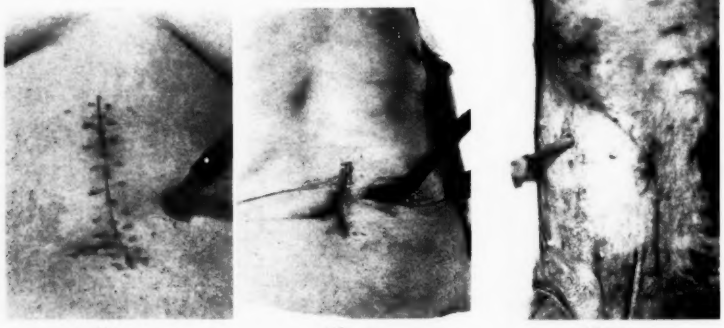

Fig. 7. Fig. 8. Fig. 9.

Fig. 7. Patient E. F. Carcinoma of œsophagus. Cannula gastrostomy April 16, 1932. Photograph taken May 3, 1932, 17 days later.

Fig. 8. Patient P. S. Carcinoma of œsophagus. Cannula gastrostomy April 15, 1932. Photograph taken May 10, 1932, 25 days later.

Fig. 9. Photograph showing the absence of corrosion about the cannula used for a Pavlov pouch fistula in a dog, duration 8 months.

angiostomy experiments on lower animals. The distal end of the cannula is now brought through the abdominal wall by means of a stab wound, preferably 2 or 3 inches from the abdominal incision. To facilitate its passage through the abdominal wall and to secure a tight fistula, a sharply pointed cap may be screwed to the distal end of the cannula. This is, of course, immediately replaced by the blunt cap or the rubber tube adapter for convenient syringe feeding. It is advisable to wrap a gauze strip about the protruding shaft until the stomach and omentum have become firmly adherent to the abdominal wall. Patients experience surprisingly little inconvenience from the cannula and have no difficulty in the introduction of semi-solid food and fluids. There is no leakage, no excoriation of the surrounding skin, and hence no necessity for the constant changing of dressings.

To date we have employed this technique for the production of a gastrostomy in 6 patients suffering from carcinoma of the œsophagus with stenosis. The legends accompanying the photographs give in sufficient detail the histories in these cases.

more rigid test of the method has been secured in its use for the production of various types of gastric and pancreatic fistula in lower animals. Under these conditions a much more irritating fluid is drained away and a satisfactory adjustment of dressings cannot be obtained. Nevertheless during the past 4 years, it has replaced other methods in our laboratory, as incomparably more convenient in affording water tight fistulæ for the quantitative collection of secretions and in its complete freedom from digestion of the skin of the abdominal wall. Here again the accompanying photographs best illustrate the technique employed.

LEIOMYOMA OF THE JEJUNUM

CLAUDE F. DIXON, M.D., F.A.C.S., AND J. A. STEWARD, M.D., ROCHESTER, MINNESOTA
Section on Surgery, The Mayo Clinic

BENIGN tumors of the small intestine are sufficiently rare to deserve reporting. The series of cases from The Mayo Clinic reported by King in 1917 contained only one benign tumor of the small intestine in more than 44,000 cases in which laparotomy had been performed, and Mallory in 4,165 postmortem examinations, found only 11 such tumors.

The types of benign tumors found in the small intestine are polyp (adenoma), lipoma, fibroma, myxoma, myofibroma, myxofibroma, myoma, neurofibroma, angioma, endothelioma, and teratoblastoma (5,13,20). The relative frequency of the different types is still in doubt. Polyps are said to be the most common (5), but the probable tendency of these tumors to disappear spontaneously (1, 2) in some cases and their definite relationship to malignancy (17, 20) make their classification somewhat uncertain. Of the other benign tumors, lipomata, myomata, and fibromata are the most common; the remainder are extremely rare. Despite the report of King that myomata occurred in his series more frequently than lipomata (45 of the former and 29 of the latter), the series of Kasemeyer in which lipomata were twice as common as either myomata or fibromata in causing intussusception, the 104 cases of lipomata reviewed by Derocque as compared with 45 cases of fibromata reviewed by Clifton and Landry, and 58 intestinal myomata reported by Hake, lead to a different conclusion. Although there are no conclusive data on the

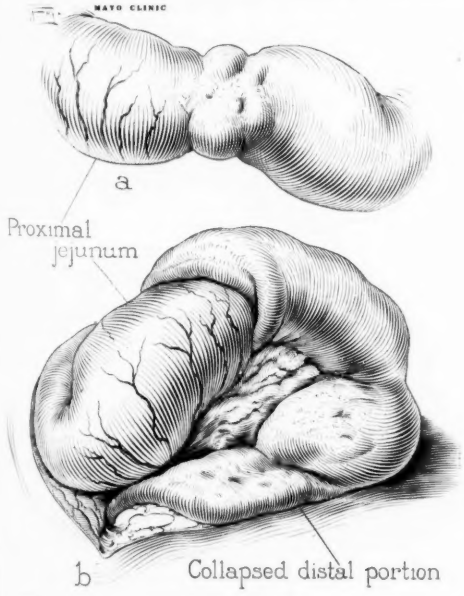

Fig. 1. *a*, Intussusception of jejunum; *b*, jejunum and tumor after reduction of intussusception.

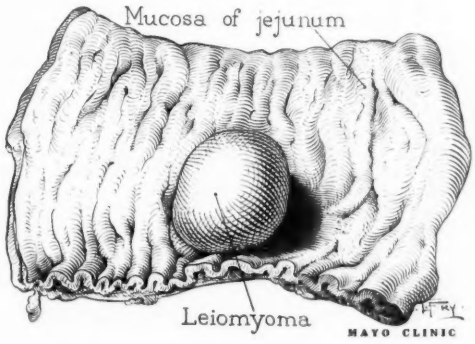

Fig. 2. Leiomyoma which extended into the lumen of the jejunum.

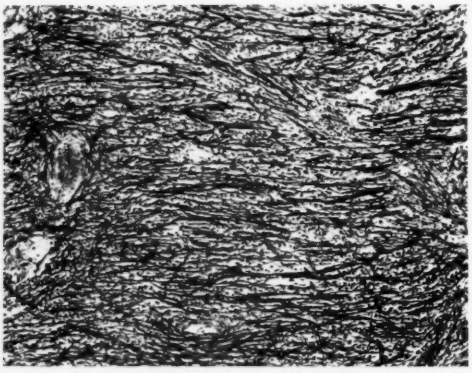

Fig. 3. Section of leiomyoma stained by van Gieson contrast method to show smooth muscle.

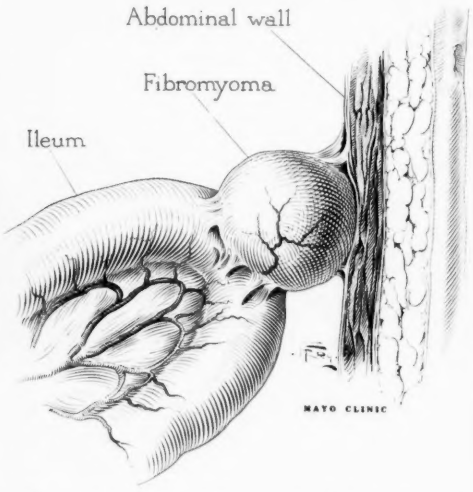

Fig. 4. Leiomyoma of jejunum attached to scar in abdominal wall.

subject, we believe that lipomata occur with about twice the frequency of either myomata or fibromata. If myxomata are included with fibromata, to which they are generically similar, the incidence of fibromata and myomata is about the same, although the question is still in dispute (12). It must be remembered that in the various cases reported the tumors were examined by many pathologists using various staining methods, and if it were possible for all the specimens to be examined by the same person with uniform stains, the resulting ratios might be entirely different, or might substantiate the term "fibroid" as used by Bland-Sutton, or the more accurate term "leiomyoma" as used by Rieniets for the small benign tumors of the stomach.

REPORT OF TWO CASES

CASE 1. A man, aged 57 years, came to the clinic December 3, 1931. He complained chiefly of a painful mass in the abdomen. The trouble had begun in April, 1931, as an occasional knife-like pain before stool. The attacks became more frequent and for the previous two and a half months had occurred 10 to 15 minutes after eating and were accompanied by the formation of a mass. The mass in the abdomen would shift from left to right and disappear when massaged. There had been neither nausea nor melena, but much eructation and borborygmus.

General examination showed the abdomen to be tender at the left of the umbilicus; an indefinite mass was palpable. Operation was advised for a tumor of the small intestine.

December 10, 1931, intussusception of the middle of the jejunum was reduced (Fig. 1), 12 centimeters of the intestine was resected and an end-to-end anastomosis was made for the removal of a tumor of the small bowel (Fig. 2). Enterostomy was made above the anastomosis. The pathologist found a leiomyoma 3.5 centimeters in diameter, showing myxomatous degeneration (Fig. 3). The patient's convalescence was uneventful and he was dismissed December 23.

CASE 2. A man, aged 57 years, came to the clinic November 30, 1931, with the complaint of a sense of fullness in an operative scar. In December, 1930, he had been operated on and stated that he thought a ruptured appendix had been removed and the abdomen drained. The operation was followed by a stormy convalescence which confined him to bed for 7 weeks. Afterward he recuperated steadily but had gas pains at the site of the scar and could feel a lump in the wound.

General examination was negative except for the right rectus incision. In the center of the incision was a smooth, firm mass, about 9 centimeters in diameter, which was partially fixed; it was painful only when pulled outward from the abdominal wall. Excision of the mass was advised.

December 3, 1931, the scar and the mass were removed. The mass was incorporated in the musculature of the lower part of the jejunum and it was necessary to resect the muscle down to the mucosa to remove the tumor (Figs. 4 and 5). The appendix was atrophic but otherwise normal. The pathologist reported degenerating leiomyoma (Fig. 6) of the jejunum (6 by 4 by 4 cm.) attached to the abdominal wall. Convalescence was uneventful and the patient was dismissed December 21.

The etiology of intestinal fibromata (the term generally used in clinical literature for these tumors), is not known (3) and the theory of inclusion or embryonal rests (6, 14) is at present as acceptable as any other.

The position of the fibromata may be intraluminal or extraluminal, a division which Heurteaux thought to be due to the tumor arising from the submucous connective tissue in the first type or from the subserosal tissue in the second type. The most thorough report on the subject is the review of 45 cases of fibroma by Cliff and Landry. In 25 of these cases the tumor was in

Fig. 5 Tumor and attached scar of abdominal wall.

the small intestine, and in all but 2 cases was intraluminal in type. The average age of the patients affected was 39 years; most of them were between 30 and 60 years, although Willis reported the case of a fibroma in the intestine of a girl aged 8 years. The tumor occurs almost equally in the two sexes and is most common in the ileum.

The outstanding clinical characteristic of fibromata of the small intestine is that of causing intussusception. Bland-Sutton reported a case of an extraluminal fibroma causing obstruction by torsion of the intestine, but intussusception was present in 23 of the 25 cases of fibroma of the small intestine reviewed by Clifton and Landry. That benign tumors frequently cause intussusception in adults had been previously pointed out by Eliot and Corscaden, who found them to be the cause of intussusception in 60 of a collection of 300 cases. This is in contrast to malignant lesions in the small bowel. Although malignant lesions in the small bowel are by far more common

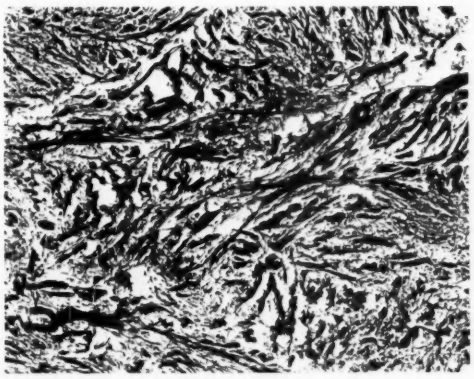

Fig. 6. Section of tumor stained by van Gieson contrast method to show smooth muscle.

(10) the incidence of intussusception is low. Judd, in reporting 24 cases of carcinoma of the small intestine observed in The Mayo Clinic prior to 1919, noted only 2 cases in which intussusception was present, and Rankin and C. W. Mayo in a report of 31 cases from The Mayo Clinic from 1919 to 1929, failed to mention intussusception as a complication. The reasons for this lack of invagination are probably the frequency of the napkin ring or circular type of carcinoma, and the comparative rapidity with which adhesions are caused in malignant cases.

The means whereby the intussusception is caused has been considered by various authors, and Iason and Filberbaum summarized the hypothesis into the following: (1) the weight of the tumor dragging the intestine; (2) violent peristalsis due to a reaction to a foreign body; (3) spasm of the intestine at the site of the tumor; (4) perverted action of muscles; and (5) paralysis of the bowel. It is probable that several of these factors enter into all cases of intussusception.

The intussusception caused by a fibroma may be acute, recurrent, or chronic, and the clinical picture will vary with the type as well as the situation of the obstructing lesion. Since the majority of these lesions are situated below the middle of the jejunum, the fulminating symptoms of obstruction high in the intestine are usually absent. In the acute cases a sudden onset of cramp-like pain and a mass in the abdomen are the best guides to the diagnosis. In Eliot and Corscaden's 60 cases of intussusception caused by benign tumor, a mass was palpable in 22. In the recurrent type a shifting abdominal tumor with the attacks will indicate the trouble. The chronic type, in which there is sufficient lumen to allow

the passage of some material, may offer the most difficult diagnosis and be indistinguishable from chronic constipation or partial obstruction from any cause. Nausea and vomiting are variable symptoms. Melena may result from an ulceration of the mucosa covering the tumor, but is not as common as in cases of intussusception among children.

Examination of the intestinal tract by the roentgen-rays must be done with great caution. In the acute type of intussusception it is manifestly contra-indicated, and in the recurrent and chronic types an acute attack with complete obstruction may be precipitated.

With the diagnosis made, surgical exploration is the treatment indicated. Although it is possible that benign tumors and whole intussusceptum may pass by way of the anus, delay in operating cannot be condoned. The operative procedure must be adopted to the case and to the surgeon's skill. Resection and an anastomosis is usually done. The operative mortality reported in the series of 25 cases reviewed by James and Sappington, and the 45 cases reviewed by Clifton and Landry, was slightly more than 27 per cent.

SUMMARY

Two cases of fibromata of the jejunum are reported. The patients were both aged 57 years. The first case was a fibromyoma of the intraluminal type, which caused recurrent attacks of intussusception. The second case was a fibroma of the extraluminal type and was attached to an abdominal scar and caused slight symptoms on pressure.

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THE ADVANTAGES OF AN EXTREME TRENDELENBURG POSITION IN OPERATIONS OF THE UPPER RESPIRATORY TRACT

JOSEPH A. PETTIT, M.D., F.A.C.S., PORTLAND, OREGON

THE reason for the occurrence of pulmonary abscess and pneumonia following operative procedures has occasioned considerable discussion. Clinical evidence and experimental evidence are often conflicting, especially the statistics of various operators who have written upon this subject. Some experimenters have reported failures to produce pulmonary abscess by the introduction of infected material into the bronchi, unless there has been some injury to the mucous membrane lining the bronchi, while others have reported a certain percentage of success. It is possible that the failure of animal experiments along this line may be due in part to the natural immunity of dogs to the infectious micro-organisms to which a human being is vulnerable.

A few writers have reported a large series of tonsillectomies with but few or no pulmonary abscesses or pneumonia following. The majority of clinicians, however, acknowledge varying percentages. It is claimed by some that pulmonary abscess following tonsillectomy is embolic in origin and does not come from aspiration. It is notable, however, that the greater percentage of pulmonary abscesses occur following operations in the upper respiratory tract and oral cavity and the majority have followed tonsillectomies. Lung abscess does not often follow drainage appendicitis and pelvic operations, or others remotely situated of a similar type from which the transference of septic emboli to the lungs should be expected.

The first reported cases were by Richardson about 18 years ago, and up to that time the attention of the profession had not been called to this possibility. Prior to that, such complications were attributed to other sources.

The frequency of the occurrence of postoperative lung abscess varies with different observers. Moore reports one in about every 2,500 tonsillectomies. Lord, in reviewing 227 cases of lung abscess, recorded that 96 were postoperative and of this number 82 per cent followed operations about the upper respiratory tract.

Various observers have made a series of bronchoscopic observations following tonsillectomies and have found aspirated blood in the trachea in a rather large percentage of cases. It is recognized that the respiratory tract rids itself of foreign particles with considerable facility if normal reflexes are undisturbed; and if the mucosa is unbroken, infection is less frequent. However, aspiration of any infectious germ or pathological tissue is a factor of risk, especially if the mucosa is broken or irritated by inhalation anæsthesia.

It is the purpose of this paper to call attention to a technique we have always used which minimizes and probably in most cases eliminates any aspiration of blood, secretions, or infective mate-

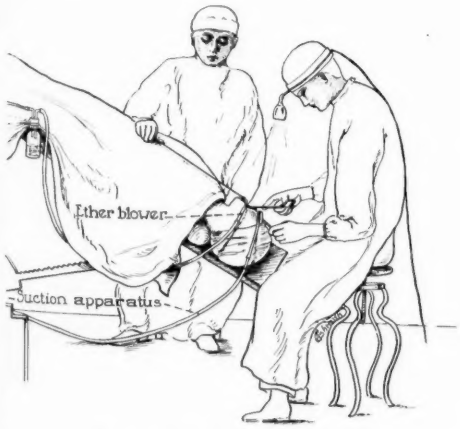

Fig. 1. Application of apparatus.

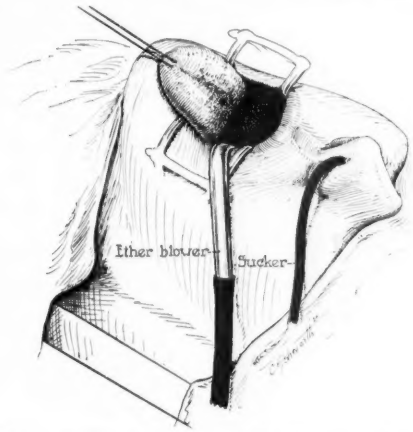

Fig. 2. Tongue depressor and hand controlled mouth sucker are used except in cleft palate cases.

rial during the general anæsthesia of surgical procedures about the upper respiratory tract. It equally minimizes deglutition during these operative procedures. While no serious consequences may follow the swallowing of blood or other material, postoperative vomiting may be increased with the bad influence of such a contamination on plastic repair in and about the oral cavity and the strain upon the stitches.

The proper use of an extreme Trendelenburg position gives many obvious advantages. First, blood, infectious materials, and secretions gravitate to the roof of the mouth and nasopharynx; in cleft palate cases gravitating into the nasal cavity and removed as described hereafter. The open air space for inspiration is *at the floor of the mouth and the lower part of the pharynx*. Sudden inspiratory efforts do not draw secretions or blood into the larynx. The unconscious efforts of swallowing find the inferior constrictor of the pharynx contracting upon an empty space. The sucker appliance as shown in the illustration constantly withdraws the accumulation of blood and débris. In cleft palate operations we have the suction apparatus connected to a fenestrated catheter which is passed through one of the nares and constantly aspirates the entire length of the nasal cavity. In operations in which the palate is intact the sucker attachment is manipulated by hand and is frequently passed into the upper part of the pharynx and across the roof of the mouth thus keeping these areas free of any accumulation. Therefore, as stated before, there is a constant free open air space at the dorsum of the tongue and in the parts of the pharynx contiguous to the laryngeal aperture.

Second, as the operator sits on a stool at the head of the patient he looks directly down upon his field of operation and gets the full benefit of the head light. He has a comfortable position for any tedious procedure, both hands can be used with equal facility and the operative field is put on a "flat surface" before him.

Third, this technique leaves both sides of the patient's head free to be occupied by assistants as the anæsthesia is given through the conventional blower and the suction appliance is brought to the field by a non-interfering single tube.

If this technique is carried out with precision the danger of aspiration pulmonary abscess or pneumonia is minimized if not eliminated. In fact during all the years we have used this we have not had a single postoperative complication of this type. We leave the patients in the Trendelenburg position or turn the face downward after the operation until all bleeding has ceased.

In conclusion we want to emphasize the importance of (1) the extreme Trendelenburg position, (2) efficient sucker arrangement to maintain the open air space at the base of the tongue and pharynx, and (3) the final cleansing of the operative field before returning the patient to bed in a position where blood or septic material may be either aspirated or swallowed.

JEJUNAL ULCER

An Analysis of Thirty-Six Cases and Study of the Literature[1]

EDWARD B. BENEDICT, M.D., Boston

JEJUNAL ulcer following gastro-enterostomy is so serious a complication and its incidence is so much in dispute that a careful review of cases proved by operation or demonstrated by X-ray examination should be of interest. Balfour's latest reports indicate an incidence of only 3.26 per cent, which contrasts sharply with figures of 20–34 per cent reported by Berg, Lewisohn, Strauss, and others. Prominent German and Austrian surgeons have for some time been advocating radical resections for peptic ulcer because of the high incidence of jejunal ulcer. Whether there is a racial difference in the size and type of peptic ulcer encountered in different countries is an interesting question. Walters and Snell gave their attention to this question last year when traveling in Europe and concluded that owing perhaps to coarse, irritating dietary habits, the type of multiple ulcers with gastritis met with in the people of central Europe seems amenable only to radical surgery, whereas the usual type of single ulcer found in France, England, and America responds well in 90 per cent of the cases to less radical surgical procedures. That diet alone is probably of great importance in the development of gastroduodenal ulcer is indicated by Bergsma's recent observations on the black people of Abyssinia, in whom the incidence of peptic ulcer is very high and whose chief article of diet from the age of 2 years is sour bread with a sauce of 50 per cent cayenne pepper!

INCIDENCE

The number of cases of duodenal ulcer for which posterior gastro-enterostomy has been done at the Massachusetts General Hospital and in which jejunal ulcer has subsequently been proved at operation in this hospital is only 7. As there have been 732 gastro-enterostomies for duodenal ulcer in this hospital the incidence of proved jejunal ulcer is practically 1 per cent. It has not been possible, however, to trace all cases. There have been 14 cases of jejunal ulcer proved by operation in this hospital in which the gastro-enterostomy was done at another hospital. To compensate for our untraced cases, these 14 may be added, making 21 cases of proved jejunal ulcer. If we still use 732 gastro-enterostomies as a basis, the incidence of jejunal ulcer is 2.9 per cent. If 15 more cases of probable jejunal ulcer, diagnosed clinically and by X-ray are added, the incidence of jejunal ulcer is nearly 5 per cent. The latter figure, however, is almost certainly too high for it includes unproved cases as well as cases in which the gastro-enterostomy was performed at another hospital. Taking the incidence of 2.9 per cent as most likely to be correct, we find it in close agreement with Balfour's latest figure of 3.26 per cent.

AGE

The age incidence of course depends considerably on the age at the time of the gastro-enterostomy. The youngest patient in this series (Case 1) was only 18 years of age at the time of gastro-enterostomy and only 21 at the time of recurrence of ulcer symptoms. At the age of 24 years a secondary operation was done and jejunal ulcer demonstrated. The oldest patient (Case 3) was 56 years old at the time of gastro-enterostomy; 5 years later this patient required repair of a gastrojejunocolic fistula. In general jejunal ulcer occurs during the middle period of life, the average age at the time of the secondary operation being 43 in this series. According to Smyth gastrojejunal ulcer has been reported in a baby 2 years old after gastro-enterostomy for pyloric stenosis and also in a patient of 81 years after gastro-enterostomy for ulcer.

SEX

Jejunal ulcer, like gastroduodenal ulcer, is largely a disease of men, only one woman being found in this series. Balfour reported 270 cases with only 22 women. That average gastric acidity is higher in the normal male than in the normal female has been shown by many observers and confirmed recently by Lerman, Pierce, and Brogan. This may be of significance in the high proportion of males having gastroduodenal and jejunal ulcer.

ETIOLOGY

Primary jejunal ulcer. Jejunal ulcer is for all practical purposes an artificial disease secondary to gastro-enterostomy. Richardson, however, was able to collect 10 cases of primary jejunal ulcer from a complete review of the literature, adding to the report 2 cases which occurred in the Massachusetts General Hospital. The etiology

[1] From the Massachusetts General Hospital.

of these rare primary jejunal ulcers is not known.

Gastrojejunal ulcer. A distinction should be made in postoperative ulcer between *gastrojejunal* ulcer which occurs exactly at the line of suture, and *jejunal* ulcer which occurs a few centimeters away from the stoma, usually in the efferent loop. In the former it is the generally accepted belief that the use of non-absorbable suture material plays a major rôle in the etiology. This point has been well established experimentally by Gronnerud, who performed gastro-enterostomy on several hundred dogs, finding secondary gastrojejunal ulcer common when silk sutures were used, but uncommon when absorbable sutures were used. Clinical experience substantiates these observations.

Secondary jejunal ulcer. The etiology of postoperative jejunal ulcer, occurring a few centimeters from the anastomosis, is not so clear. A number of theories will be discussed.

Hyperacidity theory. Hyperacidity is probably the most important factor. Acid gastric juice impinging constantly on jejunal mucosa unaccustomed to receive it might reasonably be expected to cause trauma and to predispose to ulcer formation. In support of this theory are a number of clinical and experimental observations:

1. Jejunal ulcer is almost unknown after gastro-enterostomy for carcinoma of the stomach. Key, however, did report a case of jejunal ulcer after partial gastrectomy and anterior gastro-enterostomy for carcinoma. The gastric acidity was not studied in this case and may have been high after resection. Judd also mentioned a case which occurred at the Mayo Clinic after resection for cancer. No cases have been found in the literature occurring after simple anterior or posterior gastro-enterostomy for carcinoma. This would seem to be of significance in view of the usual anacidity or hypoacidity in gastric cancer. It might be argued that such patients do not live long enough to develop jejunal ulcer, but they may survive 6 months or more after gastro-enterostomy, in which length of time it is possible to develop an anastomotic ulcer.

2. Jejunal ulcer is much more common after anterior gastro-enterostomy or after the Roux gastro-enterostomy en Y, than after posterior gastro-enterostomy (Montgomery, Gosset, Moynihan, Paterson). The explanation seems to be that in gastro-enterostomy by the anterior method a long jejunal loop is used, thus making the stoma a long way from the neutralizing effect of the alkaline duodenal contents. Furthermore, when an entero-enterostomy is also performed, as is usually the case in anterior gastro-enterostomy, the alkaline juices are likely never to reach the site of anastomosis at all. Likewise in the gastro-enterostomy en Y there is very little possibility of neutralization in the jejunum near the stoma. In spite of the relative frequency of secondary jejunal ulceration after anterior gastro-enterostomy for ulcer, we have observed above that it is never seen after gastro-enterostomy for carcinoma, where the anterior operation is so common.

3. Jejunal ulcer is very much more common after gastro-enterostomy for duodenal ulcer than after gastro-enterostomy for gastric ulcer. Balfour in a study of 139 cases of jejunal ulcer occurring in cases in which the original gastro-enterostomy had been done at the Mayo Clinic, found 130 followed gastro-enterostomy for duodenal ulcer, and only 9 followed gastro-enterostomy for gastric ulcer. In 381 cases of gastric ulcer operated on at the Massachusetts General Hospital since 1908, jejunal ulcer has not been observed to follow gastro-enterostomy in any case. Many more cases of duodenal ulcer show hyperacidity than do cases of gastric ulcer, as has been shown by Kalk at von Bergman's clinic and Hurst and Stewart in London hospitals. Quoting from Lindau and Wulff, Hurst and Stewart's figures show hyperacidity in 61 per cent of cases of duodenal ulcer and in 32 per cent of cases of gastric ulcer; and Kalk's figures indicate hyperacidity in 75 per cent of cases of duodenal ulcer, and in only 29 per cent of cases of gastric ulcer.

4. Morton and Graham have reported the case of a patient who after cholecystectomy and drainage of the common bile duct died suddenly 24 days after operation of hæmorrhage from a duodenal ulcer which had apparently formed as a result of stones impacted in both the common bile duct and the pancreatic duct with complete blockage of these secretions. As no ulcer was found at the time of the cholecystectomy, the conclusion is that it developed as a result of the failure of the alkaline secretions to enter the duodenum and neutralize the gastric juice. Thus the neutralization of gastric acidity is shown to be of importance for the protection of duodenal as well as jejunal mucosa. Holzweisser's case, cited by Hauser, is very similar, eight erosions and ulcers of the jejunum occurring in a woman of 58 years with an obstructed ampulla.

5. Jejunal ulcer is rare in women, there being only one case in this series and relatively few in the literature. Sherren has noted this and the lower gastric acidity in women, believing that this indicated the importance of hyperacidity in jejunal ulcer formation.

6. Experimentally in dogs, Mann and Williamson, and later Morton, have anastomosed the jejunum directly with the stomach, shunting the duodenal secretions into the ileum—so called surgical duodenal drainage. When this is done, a typical peptic ulcer invariably develops in the jejunum close to the pylorus where the acid gastric juice impinges upon it. When the alkaline duodenal secretions are restored to this area the ulcer heals.

7. Ivy and Fauley have shown, by performing surgical duodenal drainage in dogs and leaving an inch or so of duodenum attached to the pyloric end of the stomach, that ulcer always develops in the jejunal mucosa and not in the duodenal mucosa, although the latter is subjected to the same force of impinging gastric juice. This seems to indicate that, under the same conditions, jejunal mucosa itself is more susceptible to ulceration from the action of gastric juice than is duodenal mucosa.

8. Elman and Hartmann, by continuous external drainage of the pancreatic secretion in dogs, have shown that duodenal ulcers develop constantly under such conditions, indicating the importance of the pancreatic secretion in neutralizing the acidity of the gastric juice and protecting the duodenal mucosa.

9. Further evidence of the importance of the acidity of gastric juice in ulcer formation is brought forth by Lindau and Wulff, who call attention to ulcer of Meckel's diverticulum in which gastric mucosa with fundus glands can be demonstrated, and in which the presence of free hydrochloric acid has proved to be a regular finding. These authors point out that peptic ulcer is found in the œsophagus, cardia, area of pyloric glands, duodenum, jejunum (postoperatively), and in Meckel's diverticulum, and that in all these areas there is activity of hydrochloric acid, which they regard as of very great importance in etiology.

10. Rivers and Wilbur have recently called attention to gastro-ileac ulcers following the unfortunate surgical error of gastro-ileostomy when gastrojejunostomy was intended. They conclude that "clinical evidence is suggestive that the potentiality for the development of peptic lesions arises whenever and wherever any segment of intestinal mucosa is exposed to the eroding action of the gastric chyme."

11. Morton found by passing duodenal tubes in 23 patients with peptic ulcer that all showed free hydrochloric acid in the duodenum, whereas 13 persons without peptic ulcer did not show free hydrochloric acid in the duodenum.

12. Goldberg has recently called attention to experimental peptic ulcer formation in dogs in which a section of ileum has been used to form a permanent external fistula from a gastric pouch. The pure gastric juice acting on the mucosa of the ileum is apparently the important factor in ulcer formation in these animals.

Theory of infectious origin. Another factor which may be of significance in jejunal ulcer formation is infection. It is impossible to evaluate its importance, but it is reasonable to state that no medical treatment of peptic ulcer is complete without attention to foci of infection such as teeth, tonsils, appendix, gall bladder, prostate, and cervix, to which Moynihan adds that in performing gastro-enterostomy a diseased appendix or gall bladder should be removed. In this connection I will quote Wilkie's views on peptic ulcer: "The prevalence of dental infection is to my mind the most important single factor in determining the frequency of peptic ulcer. . . . In many of these cases we recover from the pyorrhœal pockets the same streptococcus as we find in the ulcer. . . . The combination of an ulcer in the stomach or duodenum or both with infection in both gall bladder and appendix is quite common. All these lesions must be dealt with if complete and lasting relief is to be obtained." In this connection Wilkie cites a case of jejunal ulcer with associated inflammation of the appendix and gall bladder. Streptococcus viridans was grown in pure culture from regional lymph glands from all three sites, and when this streptococcus was injected into rabbits both duodenal ulcer and cholecystitis were produced!

Other factors in the etiology of gastrojejunal and jejunal ulcer are related (1) to *general medical management*, such as diet, smoking, use of alcohol, etc., or (2) to *faulty surgical technique*, such as the use of non-absorbable sutures, too small a stoma, badly placed stoma, or (3) to *improper selection of cases*. The importance of proper medical care after gastro-enterostomy is generally recognized, though it is difficult to know for how long a period a strict diet should be followed. Many patients after a few months on a careful regimen find that they can return to normal dietary habits without ill effect. Others have to be careful to avoid highly acid fruits, meat, and fried or rich foods, and of course some have to be still more careful to live on a very bland diet. Excessive use of tobacco or alcohol should be avoided, though some patients tolerate them. Faulty surgical technique seems to be an obvious factor in etiology. Gastrojejunal ulcer with small pieces of silk or linen suture material hanging from its center has been

TABLE I.—SUMMARY OF PROVED JEJUNAL ULCER CASES

Jejunal Ulcer Proved at Operation

Case No. Identification	Sex Age at time of P.G.E.	Date of P.G.E. Duration of med. treatment	Obstruction by X-ray	Total acidity**	Suture material used in P.G.E.	Type of operation	Appendectomy	Symptom-free after P.G.E.
Posterior Gastro-Enterostomy Done at Massachusetts General Hospital								
1 *E.H.T., 251174	M 18	1917 2½ years, doubtful	None	83 c.cm.	Linen, chromic catgut	P.G.E. with infolding	Yes	3 yrs., 9 mos.
2 T.S., 294731	M 23	1928 6 wks.	None	72 c.cm.	Catgut	P.G.E. for perforating duodenal ulcer; entero-enterostomy for malfunctioning P.G.E.	No	Between 3 and 8 mos.
3 T.M.D., 250975	M 56	1922 None	Not stated	83 c.cm.	Catgut	P.G.E. for? carcinoma of pancreas to anticipate obstruction	No	4 yrs.
4 D.J.S. 283393	M 50	1919 5 mos.	None	64 c.cm.	Deep: chromic catgut	P.G.E. for perforation	No	3 yrs.
5 *M.E., 280695	M 40	1915 2½ mos.	None	99 c.cm.	Linen, chromic catgut	P.G.E. for perforation	No	2 yrs.
6 O.L.K., 318325	M 34	1917 4 wks., doubtful	Yes, marked at the only pre-operative examination	70 c.cm.	Linen, catgut	P.G.E.; ulcer not infolded	1909	1 yr.
7 W.R.E., 282299	M 38	1916 None	1913: no 6 hr. residue. 1916: medium 6 hr. residue	130 c.cm.		Plication of ulcer; P.G.E.	No	9 yrs.
Posterior Gastro-Enterostomy Done at Various Hospitals								
8 A.E.S., 312775	F 44	1923 None	Yes	Not stated	Chromic catgut, outer layer silk	P.G.E.	1908	6 yrs.
9 L.J., 316676	M 29	1913 2 yrs.	Not stated	Not stated	Not stated	P.G.E.	No	18 yrs.
10 W.H.H., 286432	M 25	1913 Not stated	Not stated	Not stated	Not stated	P.G.E.	1911	14 yrs.
11 L.W.Y., 300634	M 43	1924 None	Not stated	Not stated	Not stated	1924: P.G.E., 1927: Pylorectomy	No	2 yrs., 10 mos.
12 Z.J.C., 266967	M 24	1927 5 yrs.	No	70 c.cm.	Not stated	Posterior Pólya	No	10 days
13 W.D.S., 303753	M 42	1927 1 yr., doubtful	Not stated	Not stated	Not stated	P.G.E.	No	2 wks.
14 A.T., 266354	M 42	1911 Not stated	Not stated	Not stated	Not stated	P.G.E., short loop, Mayo method	No	3 yrs.
15 *W.H.S., 280100	M 39	1919 None	Not stated	Not stated	Not stated	P.G.E., no ulcer found	1907	Not stated

P.G.E. Posterior gastro-enterostomy.

*Cases 1, 5, 15, 17, and 20 have been previously reported by Davis, Lincoln—Surg., Gynec. & Obst., 1927, liv, 291.

**The total acidity is given in c.cm. of 0.1 normal sodium hydroxide 1 hour after test meal. In all cases prior to 1926, histamine was not used. In practically all cases for the past 5 or 6 years, histamine has been used.

***Reported by courtesy of Dr. A. W. Allen.

TABLE I.—SUMMARY OF PROVED JEJUNAL ULCER CASES

Jejunal Ulcer Proved at Operation

Recurrent symptoms	X-ray suggestive of jejunal ulcer	Total acidity**	Date of operation for jejunal ulcer	Type of operation for jejunal ulcer	Result
Posterior Gastro-Enterostomy Done at Massachusetts General Hospital					
Pain in epigastrium; melena	Showed contracted stoma	Not stated	(1) 3–17–23; (2) 11–1–23	(1) Excision. (2) P.G.E. undone	(1) Not relieved. (2) Several hæmorrhages from duodenal ulcer. Symptom-free past 8 yrs. on milk diet only
Hæmatemesis; melena; pain to left of umbilicus	Yes	Not stated	1929	P.G.E. and entero-enterostomy undone	Fairly well on medical treatment past 2 yrs. Seen: 2–9–32
Melena; distress after meals; pain in epigastrium, diffuse, reaching to umbilicus	Yes; gastrojejunocolic fistula	2 c.cm.	1927	Closure of gastrojejunocolic fistula and G.E. with excision of jejunal ulcer	Died 13 days after operation—peritonitis
Hæmatemesis; melena; pain in midepigastrium occasionally radiating to left inguinal region	Yes	104 c.cm.	1927	Subtotal gastrectomy, Shoemaker method	Doubtful improvement. Died 18 mos. after operation, after amputation both legs for arteriosclerotic gangrene; also had tertiary syphilis and tabes
Hæmatemesis; melena; epigastric pain	Yes	Not stated	1926	Excision of gastrojejunal ulcer; resection of stomach; Pólya anastomosis	Feeling very well and eating almost everything. Seen: 3–1–32
Asthenia; diarrhœa; melena	Yes, gastrojejunocolic fistula	60 c.cm.	1932	Undoing of P.G.E., closure of fistula	Gaining weight and doing well 3–22–32. Needs further operation 6–32
Anorexia; melena; vomiting; dull pain under right costal margin	Yes	67 c.cm.	1927	Separation of G.E.; pylorectomy, Pólya method; 2–5 of stomach removed	Patient writes that he is unrelieved. Has pain relieved by hot milk, nausea, vomiting, and gas 3–29–32
Posterior Gastro-Enterostomy Done at Various Hospitals					
Epigastric pain as before P.G.E.; most recent abdominal pain at left, steady; hæmatemesis; melena	Yes	72 c.cm.	1931	Gastric resection; posterior Pólya anastomosis	Relieved, gaining weight 7–16–31
Pain at umbilicus, radiating down toward pubis; asthenia	Yes	10–9–31: O.; 10–28–31: 52 c.cm.	1932	P.G.E. undone; Heineke-Mikulicz pyloroplasty	Feeling well 4 mos. after operation. Vomiting, hæmatemesis. Gastroduodenostomy Feb. 1933
Vomiting; pain in l.u.q., over most of left abdomen; "lump" in l.u.q.; diarrhœa; loss of weight and weakness	Yes, gastrocolic fistula	50 c.cm.	1927	Subtotal resection of stomach; anterior Pólya; resection of transverse colon and end-to-end anastomosis	Died 1930, cause unknown
Pain similar to that before P.G.E., starting in epigastrium, spreading to loins and chest; hæmatemesis; melena	No	94 c.cm.	1929	Resection of stomach; gastrojejunostomy (Pólya)	Feeling well and eats almost everything. Seen: 3–1–32
Lower abdominal pain; hæmatemesis; melena	No X-ray taken	Not stated	(1) 7–22–29 (2) 7–27–29	(1) Resection of jejunum. (2) Anterior Pólya resection and entero-enterostomy	Symptom-free on 5-meal bland diet. Seen: 2–17–31
Pain in l.u.q., radiating to lower quadrants and back, umbilicus and lower epigastrium; melena	Yes	1–4–29: 16 c.cm.; 3–21–30: 65 c.cm.	1930	Resection of jejunum with ulcer; anastomosis of jejunum; P. G.E.	Died 6 days after operation of general peritonitis and hæmorrhage into stomach
Hæmatemesis; melena; epigastric pain; gas and burning after meals	Yes	11–26–14: 61 c.cm.; 11–14–16: 28 c.cm.	1915	Excision of gastrojejunal ulcer	Return of symptoms 10 mos. postoperative; weakness and anæmia. 11 yrs. later, ? malignancy of liver
Diarrhœa and vomiting; no pain	Gastrocolic fistula	90 c.cm.	1926	Repair of colic fistula; closure of jejunal stoma; resection of pyloric third of stomach; Pólya anastomosis of stomach and jejunum; colostomy	Very satisfactory. Seen: 3–15–32

P.G.E. Posterior gastro-enterostomy.

*Cases 1, 5, 15, 17, and 20 have been previously reported by Davis, Lincoln—Surg., Gynec. & Obst., 1927, liv, 294.

**The total acidity is given in c.cm. of 0.1 normal sodium hydroxide 1 hour after test meal. In all cases prior to 1926, histamine was not used. In practically all cases for the past 5 or 6 years, histamine has been used.

***Reported by courtesy of Dr. A. W. Allen.

TABLE I.—SUMMARY OF PROVED JEJUNAL ULCER CASES—Continued

Jejunal Ulcer Proved at Operation

Case No. Identification	Sex Age at time of P.G.E.	Date of P.G.E. Duration of med. treatment	Obstruction by X-ray	Total acidity**	Suture material used in P.G.E.	Type of operation	Appendectomy	Symptom-free after P.G.E.
Posterior Gastro-Enterostomy Done at Various Hospitals								
16 F.A., 209832	M 26	1912 None	Not stated	Not stated	Linen	P.G.E.	No	Never symptom-free
17 *E.P., 263480	M 20	1922 None	Not stated	Not stated	Not stated	Excision of ulcer; P.G.E.	1917	6 mos.
18 ***L.A.S., B.M.6929	M 53	1930 Not stated	Yes	Not stated	Not stated	P.G.E.; entero-enterostomy; appendectomy	Yes	2 yrs.
19 L.C.S., 255344	M 31	1918 3 wks.	Not stated	Not stated	Not stated	G.E.	No	2 yrs.
20 *A.F.M., 242597	M 43	1914 Not stated	Yes	Not stated	Linen	G.E. for ? Carcinoma of stomach	No	6 yrs., 9 mos.
21 J.T., 321909	M 37	1925 Not stated	Not stated	Not stated	Not stated	P.G.E.	1919	2 yrs.

P.G.E. Posterior gastro-enterostomy.
*Cases 1, 5, 15, 17, and 20 have been previously reported by Davis, Lincoln—Surg., Gynec. & Obst., 1927, liv, 294.
**The total acidity is given in c.cm. of 0.1 normal sodium hydroxide 1 hour after test meal. In all cases prior to 1926, histamine was not used. In practically all cases for the past 5 or 6 years, histamine has been used.
***Reported by courtesy of Dr. A. W. Allen.

repeatedly reported. That trouble may follow too small a stoma is also evident, though it is not always possible to say whether a small stoma has led to ulcer formation or whether an ulcer has formed first, leading to contraction of the stoma. In one of the cases in this series (Case 9) a high stoma with jejunal ulcer was found, and yet this patient had been well for 18 years after gastro-enterostomy! It seems likely that factors other than the poorly placed stoma must have been at work in this case to bring about a recurrence 18 years later. Regarding the proper selection of cases for gastro-enterostomy, it is well known that the poorest results follow this operation when it is performed in cases in which the diagnosis is not positively established, or in which insufficient medical treatment has been followed.

A study of the 36 cases tabulated in this series brings out the importance of the various etiological factors mentioned. The lack of sufficient medical treatment before operation is an outstanding feature in almost every case. Of course, the three (Cases 2, 4, and 5) that perforated after only a short period of medical treatment required immediate operation but should not have been subjected to gastro-enterostomy at that time, particularly as in addition to their very short dietary regimen both showed hyperacidity and no pyloric obstruction by X-ray. In such cases simple suture of the perforation should be sufficient, with gastro-enterostomy later if indicated. Next in importance would appear to be pre-operative hyperacidity, almost all the cases ranging in the upper limits of normal or definitely higher. Wilkie considers hyperacidity of such great importance in jejunal ulcer formation that in such cases he performs gastroduodenostomy rather than gastro-jejunostomy. Secondary ulceration after gastro-duodenostomy occurs very rarely if at all, the stoma being placed near the ampulla of Vater, where the acid is quickly neutralized by the pancreatic juice. The postoperative gastric acidity, in the presence of jejunal ulcer, appears to be a very variable quantity, depending probably on the neutralization at any given moment by duodenal secretions entering through the stoma. In

TABLE I.—SUMMARY OF PROVED JEJUNAL ULCER CASES—Continued

Jejunal Ulcer Proved at Operation

Recurrent symptoms	X-ray suggestive of jejunal ulcer	Total acidity**	Date of operation for jejunal ulcer	Type of operation for jejunal ulcer	Result
Posterior Gastro-Enterostomy Done at Various Hospitals					
Epigastric pain; nausea; vomiting; gas and sour eructations	No	Not stated	1916	Separation of P.G.E.; resection of jejunum; linen suture found in jejunal ulcer	Died 3 weeks after operation with discharging wound and pulmonary complications
Epigastric pain 2–3 hr. after meals, relieved by food and soda; vomiting; loss of weight	Yes. Stoma closed	35 c.cm.	1924	Undoing of old P.G.E.; excision of jejunal ulcer	Symptoms returned 3 wks. after operation; re-entry 8 mos. later with operation for recurrent duodenal ulcer: partial gastrectomy and P.G.E.
Pain in epigastrium radiating to whole abdomen; nausea and vomiting	No report	Not stated	1932	Suture of perforated ulcer of jejunum	Good postoperative convalescence, 7–8–32
Pain in lower abdomen at night and 3–4 hours after meals, relieved by food and vomiting; pain at umbilicus 2–5 hrs. after evening meal	Yes	55 c.cm.	1923	Closure of G.E.; excision of gastrojejunal ulcer; gastroduodenostomy	Symptom-free 3 mos. after operation, then recurrence of epigastric pain and vomiting, treated in hospital 12 days, diagnosed probably recurrence of original ulcer, medical treatment advised
Epigastric pain on right, no definite relation to meals, relieved by soda, heat, or vomiting; gas; anorexia	Yes. Stoma closed	50 c.cm.	1921	Closure of subacute perforation of duodenal ulcer; renewal of old G.E. for gastrojejunal ulcer	Feeling pretty well, but some upper abdominal pain every 2–3 weeks, relieved by soda; can eat any food. Seen: 1–19–32
Pain over pubis, radiating to back; later pain in upper left abdomen, non-radiating; distention; relieved by food; diarrhœa	Gastrocolic fistula	45 c.cm.	1932	Excision of ulcer; lysis of P.G.E.; suture of colon, stomach, and intestines	Discharged from hospital o.k., 7–7–32. No further follow-up

P.G.E. Posterior gastro-enterostomy.
*Cases 1, 5, 15, 17, and 20 have been previously reported by Davis, Lincoln—Surg., Gynec. & Obst., 1927, liv, 294.
**The total acidity is given in c.cm. of 0.1 normal sodium hydroxide 1 hour after test meal. In all cases prior to 1926, histamine was not used. In practically all cases for the past 5 or 6 years, histamine has been used.
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any case the gastric acidity is usually lowered by gastro-enterostomy, but there seems to be no definite relationship between postoperative acidity and jejunal ulcer. The relationship of the appendix to jejunal ulcer formation is not proved, but it may be significant that in most of the jejunal ulcer cases the appendix had not been removed. Eleven of the cases showed no pyloric obstruction by X-ray and although we know that many gastro-enterostomies are entirely successful even in the absence of such obstruction we feel that the most successful cases are usually those with obstruction. Five cases (6, 7, 8, 18, 20), however, showing obstruction by X-ray examination subsequently developed jejunal ulcers. Hence it is evident that gastro-enterostomy, even when performed to relieve obstruction, may result in jejunal ulcer formation. Furthermore, obstruction revealed by the X-ray is inconclusive unless shown at repeated examinations and confirmed by the clinical picture. Unabsorbable suture material was known to have been used in this series in only 6 of the operated upon jejunal ulcer cases (1, 5, 6, 8, 16, 20) (sometimes only for the serous layer); in 1 case (16) the linen suture was found at the operation for jejunal ulcer. It is probably a factor of importance when used for the mucosal stitch. Six patients (Cases 1, 2, 10, 12, 17, 32) in this series were only 25 years of age or younger, at the time of their first operation. But in addition to their youth only one of these (Case 12) had had adequate medical treatment and 3 (or all those examined) showed marked hyperacidity, so that it is impossible to say that youth is a factor in the etiology of jejunal ulcer. In general, however, it may be said that a youthful patient frequently has not had time for prolonged medical treatment, is likely to have hyperacidity, and is therefore likely to be a poor subject for gastro-enterostomy. In one case in this series (Case 3) gastro-enterostomy was performed to anticipate possible obstruction from a suspected carcinoma of the pancreas. The subsequent development of jejunal ulcer in this case emphasizes the importance of not performing gastro-enterostomy except for very definite indications. Moynihan

TABLE IA.—SUMMARY OF PROBABLE JEJUNAL ULCER CASES
Jejunal Ulcer Diagnosis Clinically and by X-ray—Medical Treatment

Case No. Identification	Sex	Age at time of P.G.E.	Date of P.G.E. Duration of medical treatment	Obstruction by X-ray	Total acidity*	Suture material used in P.G.E.	Type of operation	Appendectomy	Symptom-free after P.G.E.	Recurrent symptoms	X-ray suggestive of jejunal ulcer	Total acidity*	Result
Posterior Gastro-Enterostomy Done at Massachusetts General Hospital													
22 L.B., 294107	M	55	1928 20 yrs., doubtful	No	87 c.cm.	Chromic catgut	(1) Cautery of ulcer (1923) (2) P.G.E.	No	2 yrs., 3 mos.	Melena; constant epigastric soreness, 1½ in. to left of midline; severe, non-radiating pains on left, 2–3 hrs. after meals; pain later in lower abdomen, both sides, radiating to groin	Yes, 1931	22 c.cm.	Has pain and gas on strict diet. Treatment for ulcer necessary 3 times since operation. Letter: 5–19–32
23 W.F.F., 305642	M	40	1921 3–6 mos.	Yes	51 c.cm.	Chromic catgut, silk	P.G.E.	No	9 yrs.	Melena; epigastric distress 2 hrs. after meals; weakness and heaviness in left stomach	Yes, 1930	Not stated	Feeling very well on careful 3-meal diet. Has trouble when he goes off diet. Seen: 1–5–32
24 J.L.L., 309315	M	42	1918 None	No	112 c.cm.	Chromic catgut, silk	P.G.E.	No	12 yrs.	Melena; hæmatemesis; anorexia	Yes, 1930	Not stated	Feeling pretty well, eats almost everything, not much meat or fruit. Works full time. Seen: 3–1–32
25 M.J.S., 273270	M	30	1921 None	Yes	Not stated	Chromic catgut	(1) P.G.E., ulcer not infolded. (2) 1925: Partial resection of stomach for bleeding duodenal ulcer	No	4 yrs.	Epigastric pain, midline, gnawing, non-radiating, 2 hrs. after meals; melena	Yes, 1931	Not stated	Feeling well except for easy fatigue. Omits meat, fruit, and vegetables from diet since discharge. Seen: 12–22–31
26 H.B., 261358	M	54	1924 3 yrs., doubtful	No	90 c.cm.	Chromic catgut	P.G.E.	No	2 yrs.	Epigastric distress in a.m.; pain 2–3 hrs. after meals, left of midline, goes up under sternum	Yes, 1931	Low	Now has to be careful of diet: not much meat, fruit, cabbage, turnip. Has pain almost every day about 1 hr. after meals, relieved by milk. Seen: 12–16–31
27 E.H.T., 254031	M	33	1923 4 mos., doubtful	No (Yes, at Boston City Hospital 1–5–23)	51 c.cm.	Chromic catgut	P.G.E., pylorectomy	1915	3 yrs.	Lower abdominal pain, sharp; gas; melena	Yes, 1929	54 c.cm.	Symptom-free after 10 days medical treatment, but has definite constriction in jejunum 1 in. below stoma. Discharged on ulcer regimen, 2–19–32
28 B.S., 268907	M	28	1917 10 wks.	Yes	104 c.cm.	Chromic catgut	P.G.E.	No	7 yrs.	Frequent attacks l.l.q. pain, not related to meals, unrelieved by food or soda	Yes, 1925	68 c.cm.	Operation advised in 1925, not heard from since
29 A.L., 274900	M	35	1926 1 yr. 5 mos., doubtful	No	80 c.cm.	Chromic catgut	P.G.E.	No	6 mos.	Pain 2–3 in. to left and below umbilicus, radiating to right side, 1–2 hrs. after meals	Yes, 1929	Not stated	Has cramp-like pains at variable times, eructations of bile-stained fluid, and feels weak. May require further operation. Seen 12–22–31
30 E.G., 280885	M	46	1928 1 yr., doubtful	No	Not stated	Not stated	P.G.E.	No	1 yr., 6 mo.	Attacks of cramp-like epigastric and l.u.q. pain 2 hr. after meals; melena; diarrhœa	Yes, 1930	50 c.cm.	Some pain in region of umbilicus about 1 hr. after meals relieved by soda. Diarrhœa and melena. Seen: 3–22–32
31 M.P.W., 303097	M	52	1930 4 mos.	Yes	Not stated	Chromic catgut inside, silk outside	P.G.E.	No	9 yrs.	Continuous dull ache in stomach; later, sharp stabbing pain below umbilicus, extending across both lower quadrants; melena	Yes, 1929	Not stated	11–24–29: After 2 days medical treatment on ward became symptom-free. Not heard from since

*The total acidity is given in c.cm. of 0.1 normal sodium hydroxide 1 hour after test meal. In all cases prior to 1926, histamine was not used. In practically all cases for the past 5 or 6 years, histamine has been used.

TABLE IA.—SUMMARY OF PROBABLE JEJUNAL ULCER CASES—Continued

TABLE IA.—SUMMARY OF PROBABLE JEJUNAL ULCER CASES—Continued
Jejunal Ulcer Diagnosis Clinically and by X-ray—Medical Treatment

Case No. Identification	Sex Age at time of P.G.E.	Date of P.G.E. Duration of medical treatment	Obstruction by X-ray	Total acidity*	Suture material used in P.G.E.	Type of operation	Appendectomy	Symptom-free after P.G.E.	Recurrent symptoms	X-ray suggestive of jejunal ulcer	Total acidity*	Result
Posterior Gastro-Enterostomy Done at Various Hospitals												
32 R.A.G., 298264	M 20	1922 None	No	Not stated	Chromic catgut	P.G.E. (high), ulcer cauterized	Yes	5 yrs.	Hæmatemesis; pain in epigastrium 3 hr. after meals, lower than before P.G.E.	Yes	91 c.cm.	Medical treatment advised, 6–11–29
33 W.F.M., 303872	M 32	1918 None	Not stated	Not stated	Pagenstecher	(1) Operation for perforating ulcer (2) G.E.	No	9 yrs.	Hæmatemesis; melena; asthenia	Yes	10 c.cm.	Medical treatment advised, 1–25–30
34 E.A.R., 313220	M 38	1924 doubtful	Not stated	Not stated	Not stated	1924: P.G.E. 1929: Pylorectomy	No	2 mos.	Pain below umbilicus in midline: nausea	Yes	18 c.cm.	Progressing well on medical treatment, no pain, slight gas. Seen: 11–17–31
35 W.W.W., 237185	M 31	1917 3 mos., doubtful	Not stated	Not stated	Not stated	Excision of ulcer; P.G.E.	No	2 yrs., 3 mos.	Epigastric pain; nausea; sour eructations; anorexia	Yes	12 c.cm	Discharged unrelieved to O.P.D., 6–25–26, no follow-up
36 H.J.R., 309196	M 37	1920 5 yrs., doubtful	Yes, marked at only one examination	Not stated	Not stated	(1) Excision of ulcer; appendectomy (2) G.E.	Yes	3–4 yrs.	Midabdominal pain radiating to groins; hæmatemesis; melena	Yes	30 c.cm.	Medical treatment advised, 10–8–30

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believes that nine out of ten failures after gastro-enterostomy are the result of the operation having been performed in the absence of any organic lesion justifying it.

SYMPTOMS

The symptoms of jejunal ulcer are chiefly pain, hæmatemesis, and melena. The pain is frequently described as similar to that of the original ulcer but is usually somewhat lower down and to the left of the umbilicus, not infrequently radiating to the left groin and sometimes generalized to the lower abdomen. This low abdominal pain may be evidence of adhesions to the colon, though after a colonic fistula is established pain may not be a prominent symptom. The pain of jejunal ulcer is less likely to be controlled by soda or dietary measures than is the pain of gastric or duodenal ulcer. This may be due to the fact that the stomach empties so rapidly through the stoma that food remains in contact with the ulcer only a very short time. Hæmatemesis and melena are very constant symptoms, one or both being present in almost all our cases, though no fatal hæmorrhage occurred. Perforation into the general peritoneal cavity may occur, as happened in one case in this series (Case 18) after posterior gastro-enterostomy and entero-enterostomy; of much more common occurrence is perforation into the colon, which occurred five times in this series or an incidence of 13.9 per cent.

DIAGNOSIS

The diagnosis depends largely on the history of gastro-enterostomy with subsequent symptoms as outlined and the X-ray findings. Camp has stated recently that "in the last two years a positive roentgenologic diagnosis of gastrojejunal ulcer has been confirmed by the surgeon in 90 per cent of cases, as compared with 74 per cent ten years ago." He bases the X-ray diagnosis on "(1) the presence of an ulcer niche (which he believes can be seen in about 60 per cent of cases); (2) persistent deformity of the stomach, stoma, or jejunum; (3) the presence of a gastrojejunocolic fistula; and (4) closure of the stoma." Camp has observed jejunal ulcer as far as 15 centimeters from the anastomosis. Of 19 cases of proved gastrojejunal or jejunal ulcers in the Massachusetts General Hospital in which an X-ray examination was made the X-ray picture was suggestive in 17 cases, or 89.5 per cent. Of the 2 cases missed by the roentgenologist one (Case 16) was in 1916 when roentgen diagnosis was less accurate than it is now and the other (Case 11) was obscured by a pylorectomy. It thus seems evident that considerable reliance may be placed on an experienced

roentgenologist in the diagnosis of gastrojejunal or jejunal ulcer.

COURSE

The course of the disease is chronic with relapses and remissions. Patients may be carried along comfortably for long periods of time on careful medical management but it is doubtful if they are ever permanently cured. There are almost always periods when rest in bed is essential because of pain or hæmorrhage. A study of the results of the 15 cases treated medically in this hospital indicates that some are doing fairly well on a careful medical regimen, but that very few are symptom free. All have had severe enough symptoms to necessitate hospitalization and in several operation has been advised but not performed. Perforation into the colon is a serious and not infrequent complication. A gastrojejunocolic fistula had occurred in 5 (Cases 3, 6, 10, 15, 21) of the 21 cases in the Massachusetts General Hospital which came to operation, or an incidence of 23.8 per cent in the operated cases. Adding the cases of probable jejunal ulcer treated medically, the incidence of gastrojejunocolic fistula is 13.9 per cent in this hospital. This figure is somewhat higher than that found in the literature, the Mayo Clinic figure being 11.36 per cent. The diagnosis of such a fistula is usually easy, for, in addition to the history of gastro-enterostomy and probably of recurrent ulcer, there is likely to be loss of weight and diarrhœa with grossly undigested food in the stools, and the X-ray examination is almost sure to show filling of the stomach by barium enema.

TREATMENT

With the course and complications of this artificial disease thus outlined it would seem reasonable that, when the diagnosis is definitely established, surgery should be the treatment of choice. Each case, however, presents an individual problem, and, in general, medical treatment should be given a fair trial and may be reasonably successful in some cases for varying periods of time. Subjective symptoms, economic disability, danger of hæmorrhage or perforation are very strong arguments in favor of surgery. The disease is an artificial one produced by surgical interference and presenting very definite pathology. If a competent surgeon is available why should such a disease be allowed to continue uncured? Balfour says, "The treatment of gastrojejunal ulcer is surgical. . . . Experience emphatically teaches that when the symptoms are those of recurring ulceration, when the roentgenogram is positive, and when relief of symptoms cannot be promptly attained and maintained by medical treatment, early operation is the safest and most satisfactory method of management."

The surgical treatment of jejunal ulcer. Plastic operations at the stoma have been generally abandoned as ineffective. Under this heading is included simple excision of the ulcer with or without enlargement of the stoma, a change in location of the stoma, or the substitution of an anterior for a posterior anastomosis. All the factors which predisposed to the formation of the original jejunal ulcer are still present and such procedures usually result in the development of a new ulcer at the stoma or in the jejunum. Three of our cases (1, 13, 14) fall into this group and in none were the results satisfactory, as one required further operation 8 months later, one died 6 days after operation of peritonitis and hæmorrhage, and the other suffered a recurrence of symptoms 10 months after operation.

Resection of the stomach is of course a more formidable procedure but, if sufficient stomach is removed, is followed by good results in many cases. The stoma must be included in the resected portion and also a fairly large section of the stomach; otherwise we have left a big stomach with the pylorus excluded as in the von Eiselsberg operation, which is known to be followed by a high percentage of jejunal ulcers (C. H. Mayo, Leriche, Fohl, Montgomery, Wright, Lahey and Jordan, de Takats and Mann, von Haberer). A similar anatomical arrangement exists after pylorectomy. In three pylorectomies in this series (Cases 11, 27, 34) jejunal ulcer has developed. However, resection of a large portion of the stomach is not by any means a sure preventive of jejunal ulcer, for jejunal ulcer following partial gastrectomy has occurred in 2 cases in this series (12 and 25) and has been reported by Balfour, Starlinger, von Haberer, Gosset, Leriche, Strauss, and others. Resection was done in 8 of our 17 cases operated on for jejunal ulcer with good results in 5 (Cases 5, 8, 11, 12, 15), poor results in one (Case 7), and doubtful or unknown results in 2 (Cases 4 and 10). It is possible that the failure in Case 7 can be attributed to the removal of insufficient stomach. With no mortality in these 8 cases and 5 good results, subtotal gastric resection must be seriously considered in the treatment of jejunal ulcer. It is, however, a serious operation, and, should it fail, further operative procedures are practically out of the question.

Fortunately there are other procedures open to us in the surgical treatment of jejunal ulcer, such as undoing the anastomosis with or without some form of pyloroplasty or gastroduodenostomy.

Jejunal ulcer is clearly the result of the original operative procedure. Therefore what could be more logical than the undoing of that procedure? The objection is at once raised that if this alone is done there may be further trouble from the original duodenal ulcer. It has already been pointed out, however, that many of these cases never had adequate medical treatment in the first place, and it is not at all unlikely that in such cases medical treatment after undoing the gastro-enterostomy may control the situation. Cases 1 and 2 are examples of simply undoing the anastomosis and returning the gastro-intestinal tract to its normal state. Both of these patients are getting on fairly well now on medical treatment, one of them, however, being limited to a diet of almost nothing but milk. If, however, medical treatment has been given a thorough trial before the operation and there has been definite evidence of pyloric obstruction, it is well, in addition to undoing the anastomosis and excising the ulcer, to do some type of gastroduodenostomy or pyloroplasty. There is very good authority for such procedures. Wilkie and also Cannon have stressed the fact that some form of anastomosis between the stomach and duodenum is more physiological than gastrojejunostomy. If stricture or ulceration near the pylorus persist, Richardson has suggested that resection of the anastomosis followed by gastroduodenostomy would seem to be the ideal procedure. In discussing indications for gastroduodenostomy Balfour has included failure of posterior gastro-enterostomy due to jejunal ulcer, where he says the gastro-enterostomy should be undone and gastroduodenostomy performed. Judd has also subscribed to undoing the gastroenterostomy, excising the jejunal ulcer and performing a plastic operation on the pylorus if it seems best. Gosset believes closure of the gastro-enterostomy alone is inadequate and should be combined with a plastic operation on the duodenum according to Judd's method, which Gosset considers the best. Von Haberer, according to Best, considers the Billroth No. I the operation of choice because it is the most physiologic-anatomic. In a paper on jejunal ulcer Terry concludes that, "in view of the very few reported cases of ulcer of the duodenum following pyloroplasty or gastroduodenostomy, it would seem wise to employ these operations in suitable cases." W. J. Mayo, discussing Terry's paper, said they treated gastrojejunal ulcer by cutting off the gastrojejunostomy and doing a Finney pyloroplasty. Wright has likewise concluded that, "when secondary ulcers have formed it is best to cut off the gastro-enterostomy and restore the natural channel if necessary by a plastic operation." Under such circumstances he mentions the usefulness of gastroduodenostomy and the Finney operation. In discussing 3 cases of jejunal ulcer following partial gastrectomy (reported by Down), Balfour sums up the present trend toward more physiological operative procedures on the stomach as follows: "The surgical treatment of jejunal ulcer is not difficult if the operation is carried out as soon as the diagnosis is made. . . . Since we have seen a number of cases in which jejunal ulcers have recurred after repeated gastric resections, it seemed reasonable . . . to reunite the stomach to the duodenum rather than to continue with resections similar to those done previously. . . . I look on the procedure as having the great advantage of giving an opportunity for a normal alkali-acid balance to be maintained. . . ." When many of the leading gastric surgeons of the world thus express themselves as in favor of some form of physiologic anastomosis between the stomach and duodenum it seems surprising that such operations are not more common.

The treatment of gastrojejunocolic fistula is surgical. As there is likely to be soiling of the peritoneum where the fistula is undone, the procedure should be as simple as possible and usually consists in repairing the fistulous opening and undoing the anastomosis, restoring the gastro-intestinal tract to normal. If this alone is not successful, pyloroplasty, gastroduodenostomy, or resection may be done later. In debilitated patients, feeding by jejunostomy may be useful in preparing them for operation. Simple repair of the fistula and undoing of the anastomosis was done in 3 of our cases (3, 6, 21); 1 patient died of peritonitis 13 days after operation; the 2 others are both recent cases, but it already seems likely that one of them will require further operation because of obstructive symptoms similar to those he had before his gastro-enterostomy. It is thus evident that gastrojejunocolic fistula is a very serious condition and as it occurs in from 10 to 15 per cent of all jejunal ulcer cases, it presents a strong additional argument for early surgery in treating jejunal ulcer.

CONCLUSIONS

The incidence of jejunal ulcer proved by operation at the Massachusetts General Hospital is approximately 2.9 per cent.

Jejunal ulcer is very rare after gastro-enterostomy for gastric ulcer and probably never occurs after gastro-enterostomy for gastric cancer.

The disease is due largely to an improper selection of cases for gastro-enterostomy.

Patients likely to develop jejunal ulcer after gastro-enterostomy are (1) those on whom the operation is performed in the absence of any organic lesion justifying it; (2) those for whom there has been inadequate pre-operative medical treatment; (3) those in whom the pre-operative gastric acidity is high.

Gastrojejunal ulcer should be distinguished from jejunal ulcer, the occurrence of the former being attributable in some cases to the use of non-absorbable suture material.

The diagnosis of gastrojejunal or jejunal ulcer is usually not difficult; much weight can be put on the opinion of an experienced roentgenologist.

Hæmorrhage is common but seldom fatal.

Perforation into the general peritoneal cavity is rare, but perforation into the colon occurs in 10 to 15 per cent of the cases.

Unless prompt and permanent relief is obtained by medical management, the treatment of jejunal ulcer is surgical.

In the surgery of jejunal ulcer the least formidable and most physiological procedures should be tried first, e.g., (1) Simple undoing of the anastomosis, especially in cases where the original operation does not appear to have been justified. (2) Undoing of the anastomosis with some form of pyloroplasty or gastroduodenostomy. If these fail there still remains the possibility of (3) subtotal gastric resection, the fact being kept in mind that jejunal ulcer may occur after even fairly large portions of the stomach have been removed.

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CARCINOMA OF THE TRANSVERSE COLON

THEODORE S. RAIFORD, M.D., BALTIMORE, MARYLAND
From the Departments of Surgery and Surgical Pathology of the Johns Hopkins Hospital and University

THE literature upon malignancy of the large bowel is prodigious and there is probably no phase which has escaped attention at some time or other. The opportunity of observing a recent case of carcinoma in the mid-transverse colon which terminated very favorably, has pointed out two aspects of the condition which have perhaps not received due consideration.

It is surprising that malignant tumors of the transverse colon occur with relative infrequency. On analyzing 297 cases of carcinomata of the colon, it was found that only 22 or 7.3 per cent were located between the hepatic and splenic flexures.

It is commonly thought that due to the accessibility of this region, operative removal of such tumors is facilitated and the prognosis is good. A careful analysis of this group, however, reveals a mortality rate higher than is customarily found for growths in other parts of the large bowel. These deaths are due to various causes: some to faulty operative technique, some to unavoidable postoperative complications, and still others to the difficulty encountered in effecting a complete removal.

The 22 cases recorded in this hospital have been reviewed from the standpoints of clinical features, surgical technique, and pathology with the intent of discovering the reasons for these peculiarities.

OCCURRENCE

Table I shows the distribution of 297 tumors of the colon in its various parts. The colon is for this purpose empirically divided into five parts; the ascending colon, hepatic flexure, transverse colon, splenic flexure, and descending colon (including the sigmoid). Further subdivision seems unnecessary and ambiguous. Bearing in mind that the transverse colon is approximately the same in length as either the ascending or descending portions, it is more than accidental that carcinomata occur about one-fifth as frequently in the former location as in either of the latter. A satisfactory explanation for this characteristic is entirely lacking. There is nothing peculiar in the embryology, anatomy, or histology which might predispose to the infrequency with which it is invaded. It must be borne in mind, however, that the transverse colon is functionally more active and that stasis of fæcal contents is less likely to occur. Until the relationship between stasis, irritation, and tumor formation is established, however, this cannot be regarded as a responsible factor.

AGE—RACE—SEX INCIDENCE

Carcinomata of the transverse colon are similar in respect to these features to malignancies elsewhere in the large intestine. The age incidence is most commonly in the fifth decade of life, the average age of the group being 44 years. All of the tumors occurred in members of the white race. Fourteen occurred in males and 5 in females, agreeing closely with the sex distribution in all gastro-intestinal malignancies.

CLINICAL FEATURES

The symptoms of carcinoma in the transverse colon are not unlike the clinical manifestations of malignancies elsewhere in the gastro-intestinal tract. The average duration of symptoms is about 14 months. General symptoms experienced by the patient are malaise, loss of weight, secondary anæmia, and abdominal pain. More specific symptoms are apparent when obstruction is present, either partial or complete. The patient then complains of eructation, digestive upsets, fullness or distention, meteorism, and constipation. When ulceration has occurred, tarry stools are frequently observed.

It is interesting that the symptoms are frequently referable to upper intra-abdominal pathology. In one instance, the symptoms were characteristic of an acute cholecystitis. In several cases the symptoms and signs were mistaken for those of gastric malignancy and in none of these was the correct diagnosis made before the abdomen was opened.

The physical signs may be negligible in the early stage of the disease, and nothing more than a moderate distention observed. Tumors in this region, however, are usually palpable early and, by careful palpation, even a small mass can be picked up against the prominence of the vertebral column. The patients are usually underweight, pale, and undernourished. Laboratory examination reveals a moderate secondary anæmia. The stools in many instances are grossly black or bloody and, in the majority, occult blood can be demonstrated. Achlorhydria is commonly associated with carcinomata of the stomach. It is surprising,

TABLE I.—DISTRIBUTION OF 297 CARCINOMATA OF THE COLON

Location	Cases	Per cent
Cæcum and ascending colon	96	32.3
Hepatic flexure	21	7.1
Transverse colon	22	7.3
Splenic flexure	18	6.6
Descending colon and sigmoid	109	36.7
Location undetermined	31	10.0
Total	297	100.0

TABLE II.—METASTASES AND EXTENSION

	Cases
Metastases	
Glands	5
Liver	6
Extension	
Stomach	8
Omentum	6
Duodenum	1
Ascending colon	1
Gall bladder	1
Small intestine	2

however, to find an absence of free hydrochloric acid in a large percentage of carcinomata of the transverse colon.

Diagnosis is usually made by the X-ray films following a barium enema. These, when positive on repeated examination, should be conclusive, but it is never amiss to perform a gastro-intestinal series, as embarrassing mistakes have been known to occur following the omission of this procedure.

PATHOLOGY

The majority of tumors in this location assume the annular constricting form, sometimes aptly described as "napkin-ring" carcinoma. The early growth may appear as a small ulcer on the mucosal surface of the gut wall. The edges are hard and elevated, leaving a crater-like erosion in the center. The wall is thickened and indurated. As growth progresses, the ulcerated area extends around the bowel more rapidly than longitudinally, leading eventually to an annular growth. When this has occurred, the tumor continues to grow both longitudinally and inwardly, forming a hard, encircling band which constricts the lumen until, in late cases, it is almost entirely occluded.

Extension to the mesentery may take place. Involvement of the mesentery glands is not rare and does not seem to be dependent upon the age of the tumor. Metastases have been observed in very early cases of short duration. The liver is particularly susceptible to metastases and contained secondary growths in 27 per cent of the cases of this series. Extension to adjacent organs occurs and it is not at all uncommon to find on laparotomy a large conglomerate mass of tumor the origin of which is not determined until the specimen is dissected. Extension is particularly apt to involve the stomach, in fact this had occurred in 32 per cent of the cases, more than had metastasized to either the liver or lymph glands. This brings about complications both in diagnosis and treatment. The symptoms and X-ray findings are frequently those of gastric pathology and the correct diagnosis is not usually made before operation. Surgical treatment is more difficult since a partial gastrectomy is necessary to remove all possibly involved tissue. This extension may travel through the lymphatics of the omentum by which means a surprising number of omental implants occur. More commonly the growth involves the posterior wall of the stomach with which it is partly in contact. Table II shows the location of the metastases and secondary growths.

The microscopic pathology is not distinctive. The majority are adenocarcinomata. It is surprising that a large percentage of cases showed mucoid degeneration in the presence of the adenocarcinoma and were originally diagnosed colloid carcinoma. Such was the case in 60 per cent of the tumors, a much higher percentage than has been encountered in the other portions of the colon. The medullary and scirrhous types of carcinoma may also occur, but are far less frequent than adenocarcinoma.

TREATMENT

The treatment of carcinoma of the transverse as well as other parts of the colon should consist of early radical excision. Since this is the most easily accessible portion of the colon, the average operator regards the prognosis as good and has a tendency to exercise less care in resection. The results of surgical extirpation in 18 treated cases were not gratifying. Six died as a result of the operation, 2 of peritonitis and 4 of pneumonia, embolism, or shock. Two died of recurrence, 3 are well, 5 years or more; 3 are living without signs of recurrence less than 5 years after operation; and 4 were improved following operation but no report as to ultimate result was obtained. Four were thought to be inoperable and eventually died of extension and metastases. Fæcal fistulæ developed in 4 cases. In all of these, catgut was used in suturing the blind ends. It is the experience of several operators that heavy silk is safer than catgut at this site. Table III shows the results of treatment in this group of cases.

The anatomy of the transverse colon should be reviewed briefly before further approaching the

TABLE III.—RESULTS OF TREATMENT

	Cases
Improved following operation, but lost	4
Well less than 5 years following operation	3
Well 5 years or more	3
Dead—postoperative	
Peritonitis	2
Pneumonia	2
Emboli	1
Postoperative shock	1
Dead from recurrence following operation	2
Inoperable, palliative treatment only	4
Total	22

surgical treatment. Its general direction is transversely across the abdominal cavity with a variable degree of ventral and caudal convexity. It is supported by the transverse mesocolon, the continuation of which forms the inferior leaf of the greater omentum. This is directly overlying the colon and in approximation to it. Near the hepatic flexure, it is not entirely covered by peritoneum, but overlies the right kidney and duodenum. Near the splenic flexure the mesentery is longer and allows more mobility. The splenic flexure is higher and more posterior than the hepatic. The blood supply is furnished largely by the middle colic artery arising from the superior mesenteric. It arches to the right, supplying the hepatic flexure and ramifies in the region of the splenic flexure with the left colic. The course of the middle colic is variable, but it usually curves upward about 6 to 8 centimeters to the right of the midline.

Bearing in mind these anatomical features, the mode of surgical procedure must be approached. Two methods of removal are open to the operator, local resection and resection of the entire right half of the colon with an ileocolic anastomosis.

When the tumor is located in the middle or left half of the transverse colon, local resection may be practised with impunity inasmuch as the intestine can be mobilized and anastomosis facilitated. A common mistake of resection is the removal of too much bowel, leaving short stumps upon which considerable tension must be exerted to obtain approximation. Some pathologists claim to have found evidence of malignant change in the intestinal wall, 2 inches or more from the site of the primary growths. No doubt this may be true in advanced cases but in early operable cases this statement is open to question. It is the author's impression that the removal of a wide margin of normal gut is frequently overrated. A second and perhaps more important technicality lies in the preservation of the blood supply. Meticulous care should be exercised in choosing the point of resection so that viability of both stumps is preserved. This necessitates careful dissection of each branch of the middle colic artery which in some instances is especially difficult, due to an excess of fat in the mesentery. Therefore, three factors must be considered in choosing the point of resection, the blood supply, the mobility of the bowel, and the proximity to the tumor.

Two methods of anastomosis are available, the end-to-end and the lateral. The end-to-end method may be used in some cases with success, but in general is not as satisfactory as the lateral method. It requires more exacting surgical technique and the chance of leakage following anastomosis is greater. The operator may be governed by circumstance and if it is impossible to overlap the bowel without undue tension, the end-to-end method must be used. The anastomosis devised by Parker and Kerr is frequently used and is more satisfactory than the older open method.

Whenever possible the lateral anastomosis is preferable. A larger stoma is formed and there is less chance of obstruction. There are two satisfactory methods of performing this union. The first is the isoperistalsic anastomosis and is in general satisfactory, except for two features. Blind pouches are left, necessitating obliteration by suture to the opposing lumen. In spite of this precaution damming up of fæcal contents sometimes occurs which may cause either perforation or occlusion of the stoma. The anastomosis is dropped back into the peritoneal cavity after the operation. Should gangrene or perforation occur, peritonitis is likely to result. Bloodgood devised a method to overcome this feature in 1906. He performed an antiperistalsic lateral anastomosis, but brought the blind ends out through the peritoneum when closing the wound. This method extraperitonealizes the weak blind ends and in the event of gangrene or rupture, infection takes place outside the peritoneal cavity. Thereafter nothing more harmful than a fæcal fistula results which can be closed at a later date.

If the tumor is located in the proximal half of the transverse colon, the entire right half of the colon may be removed. The description of this technique can be found in all treatises on operative surgery and need not be repeated here. It involves freeing the cæcum and ascending colon from the peritoneal attachments and resection of the right half of the colon together with a portion of the terminal ileum. The raw surface left is then peritonealized and a lateral anastomosis performed between the terminal ileum and the distal

transverse colon. In the hands of competent operators this is a relatively safe procedure and the operative mortality is surprisingly low. It is a longer operation and consequently attended by greater shock. The removal of such a large portion of gut results in a moderate physiological disturbance of the bowel which may not become readjusted until some months after the operation. Nevertheless it is considered an excellent operative procedure both from the standpoint of radical removal of possibly involved glands and a functionally good anastomosis.

The use of radium and deep X-ray therapy has been found no more efficacious in carcinomata of the transverse colon than in other portions of the bowel, for the reason that adenocarcinomata are not radiosensitive. While it is true that irradiation may sometimes give temporary relief in late inoperable cases, it rarely brings about any lasting improvement. A short circuiting operation is more desirable for the relief of obstruction.

The prognosis of carcinomata of the transverse colon should be comparable to that of carcinomata elsewhere in the gastro-intestinal tract with observation of the above mentioned technical factors. The tendency toward invasion of the stomach jeopardizes the operability, but emphasizes the need for thorough examination including a gastro-intestinal series and barium enema whenever there are symptoms of intra-abdominal pathology. Far too frequently is the complete X-ray examination omitted either through negligence or the desire of the physician to spare the patient discomfort in the examination or a seemingly unnecessary expenditure.

CASE REPORTS

Detailed case reports all too often confuse the reader and lend ambiguity to a surgical paper. It is the author's intention to avoid this so far as possible, but with a relatively small number of cases there are certain illustrative features which can be brought out only by a brief case history. In the subsequent reports, only those features which are of direct importance in the diagnosis and treatment of the cases are included.

CASE 1. Path. No. 45848. White female, aged 52 years. The patient had complained of headaches, constipation, and weakness for 2 years. She had felt a subjective obstruction to the bowels for 2 months and had lost 18 pounds in weight during the illness. Physical examination revealed a palpable, tender mass just above and to the right of the umbilicus. The patient was markedly anæmic. An irregularity was seen in the middle of the transverse colon with the fluoroscope and in the X-ray plates. Pre-operative diagnosis: carcinoma of the transverse colon.

Operation was performed September 5, 1931. Six inches of the intestine were removed with a V-shaped piece of mesentery for a hard constricting tumor located in the middle of the transverse colon. The mesentery contained several enlarged lymph glands. The ends of the intestine were anastomosed laterally by the "thumb" method of Bloodgood. Pathological diagnosis: adenocarcinoma, grade II, with mucoid degeneration; the glands were negative for metastases. One of the blind ends broke down on the tenth day after operation with the subsequent formation of a fæcal fistula. This drained persistently for several weeks but was finally closed and the patient was discharged 3 months after operation. She is well at the present time, 8 months after operation.

This patient fortunately recognized the subjective signs of obstruction before the tumor became inoperable, thereby enhancing the chances of recovery. The advantages of the "thumb" anastomosis devised by Bloodgood are illustrated by the rupture of the blind end of bowel with a subsequent fistula. Had this occurred within the abdominal cavity, a generalized peritonitis would have developed with a probable fatal termination. The condition of this patient became critical during the operation, the blood pressure falling and the pulse rising. The operator, having a donor previously matched for blood transfusion, administered 500 cubic centimeters of citrated blood to the patient on the table, with the result that she left the table in excellent condition and suffered little postoperative shock. This measure, if practised more frequently would no doubt avert many postoperative deaths from shock after severe operations.

CASE 2. Path. No. 44223. White female, aged 56 years. The patient had suffered abdominal pain, nausea, and vomiting for 3 months and was conscious of an abdominal mass for 2 months. She had lost a moderate amount of weight. Physical examination revealed a tender, palpable mass in the midline below the umbilicus. It was the size of a grapefruit with a discharging sinus. The X-ray examination showed in the mid-transverse colon complete obstruction to the barium enema. Pre-operative diagnosis: carcinoma of the mid-transverse colon.

Operation was done December 8, 1928. A large tumor mass was found within the sac of a ventral hernia. It was resected and the hernial defect repaired. The tumor was not attached and no enlarged glands were found. Pathological diagnosis: adenocarcinoma, grade IV, with fistulous communication to the bowel. Patient died 14 days after operation from infection of the abdominal wall and pulmonary embolism.

It is unusual that a tumor giving rise to symptoms for only 3 months could have attained this size. The patient was either unaware of premonitory symptoms or the tumor grew with extreme rapidity. The coincidence of a ventral hernia with the tumor no doubt confused the patient, for having the previous condition for a number of years she in all probability attributed her symptoms to it.

CASE 3. Path. No. 38244. White male, aged 32 years. The patient had suffered moderate gastro-intestinal dis-

orders for 3 months and had lost 25 pounds. He had been conscious of an abdominal mass for 3 months. The last 3 weeks of his illness were characterized by a mucous diarrhœa of foul character. Secondary anæmia and cachexia were marked. A firm, tender, movable mass the size of a lemon was felt below the umbilicus. Pre-operative diagnosis: carcinoma of the transverse colon.

Operation was done December 8, 1928. An annular, necrotic tumor was found in the colon extending to and involving the stomach, omentum, and mesentery. The tumor was resected together with a portion of the mesentery, omentum, and stomach wall. The bowel was joined by an end-to-end anastomosis and the stomach defect was closed. Pathological diagnosis: adenocarcinoma, grades II and III, arising in the left transverse colon. Patient died 9 hours after operation from postoperative shock.

The failure of the first physician consulted to suspect the malignancy emphasizes the tremendous importance of thorough gastro-intestinal studies in all cases of obscure disorders. This calls for an extreme nicety of judgment in deciding what examinations must be made and when, since it is obvious that every case of indigestion should not be subjected to the routine examination, not only on account of the discomfort to the patient, but for economic reasons as well.

CASE 4. Path. No. 37357. White female, aged 60 years. This patient suffered from intermittent cramp-like pains for several months during which a small movable lump would sometimes be seen. Blood was seen in the stools on several occasions, and the patient had three transient attacks of jaundice. Physical examination disclosed a movable, non-tender mass about 7 by 12 centimeters in size, palpable in the upper right quadrant. There was an absence of free hydrochloric acid. A roentgenographic filling defect could be seen in the transverse colon. Pre-operative diagnosis: carcinoma of the transverse colon.

Operation was done May 18, 1925. A small tumor was found in the transverse colon which was freely movable. It was removed together with a portion of the transverse colon and a portion of the mesentery. The ends were anastomosed by the Parker-Kerr method. Pathological diagnosis: polypoid adenocarcinoma, grade II, with mucoid degeneration; no glandular metastases. Transient symptoms of obstruction appeared on the fifteenth day after operation, but soon disappeared. The patient was discharged well 3 weeks after operation. No ultimate result note was obtained.

The jaundice in this case could be caused by either the extension of the tumor to the periductal lymph nodes or a coincident and irrelevant condition. The obstruction after operation was probably due to a temporary volvulus or kink of the intestine. But its spontaneous disappearance rendered the complication of little significance.

CASE 5. The patient suffered weakness, anorexia, and hæmaturia, which led to the diagnosis of pyelonephritis and a subsequent nephrectomy which was done 4 months before present admission to the hospital. He improved slightly following this operation but suffered an exacerbation of the symptoms later with a pronounced cachexia and loss of weight. Physical examination disclosed a moderate distention of the abdomen with a rigidity of the abdominal muscles. Several indefinite masses were palpated in the upper abdomen. There was a hyperchlorhydria and a secondary anæmia. Roentgenograms showed a defect in the greater curvature of the stomach and a spastic condition of the right transverse colon. Pre-operative diagnosis: carcinoma of the stomach.

Operation was done December 8, 1924. An exploratory laparotomy revealed an inoperable carcinoma of the distal transverse colon with metastases to the liver. Pathological diagnosis: carcinoma of the transverse colon, pressing on the stomach; no specimen removed. The patient recovered from the immediate effects of the operation but died a few months later from the extension of the disease.

The presence of a kidney lesion no doubt obscured the tumor symptoms in this case. Had there been no other pathology, the gastro-intestinal condition would have been diagnosed sooner and the tumor approached while in its operable state. The hyperchlorhydria is unusual since many cancers of the large bowel are characterized by an achlorhydria. This case illustrates the frequent confusion noted in diagnosing carcinomata of the transverse colon. The roentgenographic examination indicated a lesion of the stomach but this was apparently caused by a tumor mass in the colon producing a secondary irregularity, while the absence of the typical constricting tumor in the colon left it free from roentgenographic defects.

CASE 6. Path. No. 35873. White male, aged 46 years. Intermittent lower abdominal pain had been noticed for 3 years. Exploratory laparotomy 1 year before admission revealed multiple tumors in the bowel. Following this the patient was temporarily improved but had a subsequent recurrence of symptoms with increased severity, borborygmus, nycturia, and loss of weight. Clinical examination revealed visible peristalsic waves and meteorism. A crater shaped ulcer was found in the rectum. A secondary anæmia was present and there was a roentgenographic defect in the transverse colon. Pre-operative diagnosis: carcinoma of the mid-transverse colon.

Operation was done August 4, 1924. The entire right colon was resected for a large mass arising in the mid-transverse colon and adherent to the stomach, gall bladder, and omentum. Several isolated polyps were found in the removed bowel. A lateral ileocolostomy was then performed. Pathological diagnosis: adenocarcinoma, grade III, mid-transverse colon; multiple benign polyposis. A fæcal fistula formed in the scar which refused to heal and the patient was discharged unimproved at his own request and no subsequent note has been available.

The multiple polyposis was apparently regarded by the first operator as a benign condition, and no attempt was made at operative removal. The treatment of choice would have consisted of removal of all the involved bowel, since carcinomatosis is a frequent coincident condition. Multiple carcinomata are rare and furnish the main argument in favor of malignant change in previously existing benign polyps.

CASE 7. Path. No. 32606. White male, aged 38 years. The patient had suffered weakness, loss of weight, and anorexia for 7 months with dull epigastric pain increasing in severity and frequency for 3 months. Nausea and vomiting, melena and diarrhœa were present for 1 month. Physical examination disclosed a moderate abdominal rigidity, gastric achlorhydria, and secondary anæmia. A fistulous communication between the stomach and transverse colon was visible in the X-ray plate following a barium enema. This arose at the site of a filling defect in the colon. Pre-operative diagnosis: carcinoma of the transverse colon.

Operation was done March 31, 1923. A portion of the transverse colon and a section of the stomach wall were resected for a large friable polypoid growth arising from the colon and extending to the stomach. The continuity of the colon was re-established by lateral anastomosis and the defect in the stomach closed. Pathological diagnosis: adenocarcinoma, grade II, with mucoid degeneration; glands were negative for metastases. The patient died 7 days after operation from generalized peritonitis.

When a cancer has advanced to the stage illustrated by this case the outlook is extremely poor. The operation is long and difficult and even with the most perfect technique is hazardous. This is another of the cases in which the tumor grew rapidly and involved the stomach, but in which in addition a fæcal fistula had formed.

CASE 8. Path. No. 33633. White male, aged 63 years. Alternating constipation and diarrhœa had annoyed the patient for 3 years. During this time he had sometimes been conscious of an abdominal mass. He suffered frequent attacks of colic-like pain, which were often relieved coincident with a "squirting" sensation. He had lost considerable weight. A hard, tender, movable mass the size of an orange was noticed below the umbilicus. Free hydrochloric acid in the gastric contents was not noted. A roentgenographic defect was visible in the first third of the transverse colon. Pre-operative diagnosis: malignancy of large bowel.

Operation was done August 7, 1923. A large mass arising in the transverse colon extending to the stomach and adherent to the omentum and small intestine was removed by resecting a portion of the transverse colon and a piece of the stomach wall. After separating the mass from the other involved structures, a lateral anastomosis of the colon was performed and the defect in the stomach closed. Pathological diagnosis: adenocarcinoma, grade III, with mucoid degeneration. The patient died 14 days after operation from pneumonia.

The patient's own description of his condition is oftentimes invaluable. For instance this patient stated that he felt a "squirting" sensation which relieved pain and distention. Obviously this could be caused by nothing other than partial obstruction of the bowel allowing only small amounts of fæcal material to pass at a time. Of similar value is the patient's description of a taste of hard boiled eggs following eructation and regurgitation. The flat taste of acid free stomach contents is immediately suggestive of achlorhydria. One patient complained that his clothes fitted too tightly, so that he was not able to wear his belt comfortably but at the same time he was losing weight. These features pointed to a moderate, almost imperceptible distention, but persistent and sufficient to acquaint the patient with an unnatural condition in his abdomen.

CASE 9. Path. No. 33217. White female, aged 48 years. The patient had suffered vague attacks of indigestion marked by cramping pains and bloating sensation for 1 year. At the most recent attack 1 week before admission, she vomited food material ingested 3 days previously. She had lost 15 pounds in weight. A moderate fullness of the abdomen was evident and roentgenographic filling defect was present in the left transverse colon. Pre-operative diagnosis: carcinoma of the large bowel.

Operation was done June 9, 1923. At exploratory laparotomy an inoperable carcinoma was found arising in the left transverse colon involving the stomach and adherent to the parietal wall. A palliative colocolostomy was performed. Pathological diagnosis: carcinoma of the transverse colon; no glandular metastases. The patient died in 3 months' time from an extension of the disease.

It is unfortunate that often the symptoms brought about by these cancers are so mild that the patient is not alarmed before the disease has advanced to an inoperable stage. An excision could have been attempted, but since so few cases involving the stomach wall recover, the operator displayed good judgment in doing nothing more than a palliative operation, thereby giving the patient freedom from symptoms during the remaining months of her life.

CASE 10. Path. No. 57807. White female, aged 70 years. This patient complained of constipation for 10 months, during which time, she was frequently nauseated and sometimes vomited fæcal material. Gastro-intestinal series 5 months before admission was negative. Physical examination disclosed a superficial resistance in the upper left quadrant overlying a definitely outlined mass, which was irregular in shape, fixed, and tender. There was a roentgenographic obstruction just proximal to the splenic flexure. Pre-operative diagnosis: carcinoma of the transverse colon.

Operation was done October 5, 1922. At exploratory laparotomy an inoperable tumor was found arising from the transverse colon, adherent to the jejunum and stomach. It was the size of an orange, was nodular and hard, and metastatic nodules were found in the omentum and liver. Pathological diagnosis: carcinoma of the transverse colon; no specimen was obtained. The patient died 5 months after operation from extension of the disease.

Spasticity of the colon not infrequently produces an obstruction which can be mistaken for an organic lesion by the X-ray findings alone. Therefore, it is important not only to repeat the gastro-intestinal series but to observe the patient fluoroscopically as well.

CASE 11. Path. No. 30673. White male, aged 42 years. The patient suffered from intermittent pain in the left lower quadrant and a marked diarrhœa for 8 months following an operation for acute intestinal obstruction. He was sometimes conscious of a mass in the left side during an attack. Physical examination revealed the abdomen tympanitic

and tender to palpation on the left side. A roentgenographic defect was present near the splenic flexure in the transverse colon. Pre-operative diagnosis: partial obstruction due to peritoneal adhesions.

Operation was done June 15, 1922. A tumor the size of a lemon was found in the left transverse colon attached to the stomach. It was freed and resected together with adequate normal bowel and a lateral anastomosis preformed. Pathological diagnosis: adenocarcinoma, grade I, with mucoid degeneration; no glandular metastases were found. The patient was discharged well 3 weeks after the operation.

It is remarkable that although symptoms had been present before the first operation, no tumor was found. Evidently it must have been present at that time and was overlooked at exploration. Fortunately for the patient it was of low grade malignancy and in spite of delayed removal a good result was achieved. Too much emphasis cannot be laid on the necessity of a thorough exploration at every laparotomy.

CASE 12. Path. No. 28466. White male, aged 69 years. Three years before admission a local physician had found in the abdomen a mass which had increased very little in size. Pain, jaundice, vomiting, and cachexia had been present 1 year. At physical examination an indefinite, slightly tender mass was felt in the upper right quadrant. Roentgenograms showed an abnormal position of the intestines in this region due to an extra-luminar mass. Secondary anæmia was marked and occult blood was found in the stools. Pre-operative diagnosis: malignancy of the large bowel.

Operation was done July 9, 1921. A tumor the size of an orange in the right transverse colon, was resected with a piece of mesentery containing several large glands. The bowel was anastomosed by the end-to-end method. Pathological diagnosis: adenocarcinoma, grade I, with mucoid degeneration; glands negative for metastases. Patient was well 10 years after operation.

It is difficult to understand why the first physician consulted allowed this patient to continue without hospitalization for 3 years following the first appearance of the mass. It is perhaps another case in which the patient is alarmed by symptoms of discomfort rather than the presence of an abnormal mass. A gratifying result following the removal of a mass of this duration is unusual and was no doubt due to its extremely low grade of malignancy.

CASE 13. Path. No. 28670. White male, aged 52 years. For 6 weeks this patient had suffered intermittent cramp-like pains and meteorism. Malaise and anorexia accompanied these symptoms. At physical examination indefinite peristalsic waves and a definite bulging mass at the umbilicus were visible. This mass was firm, nodular, and freely movable but not painful. Pre-operative diagnosis: carcinoma of the large bowel.

Operation was done February 25, 1921. A tumor was found in the mid-portion of the transverse colon. This was resected with 2 inches of normal bowel on either side and a V-shaped piece of mesentery including several enlarged glands. A lateral anastomosis was performed between the blind ends. Pathological diagnosis: adenocarcinoma, grade II, with mucoid degeneration; the glands showed no metastases. The patient was well 8 months after operation, but no further information was obtained.

This patient's symptoms were not severe. The neurasthenic patient usually causes the physician no end of trouble by his magnification of minimal symptoms but it is to be said in their favor that few neurasthenics die of cancer. This patient in spite of his mild symptoms sought the advice of his physician early. If every patient recognized the possible significance of premonitory symptoms the death rate from cancer would be considerably lower.

CASE 14. Path. No. 25276. White male, aged 54 years. Pain in the left side had been present intermittently for 7 months, and the patient was conscious of an abdominal mass for 4 months, before admission. The stools were frequently black and tarry. Occult blood in the stools comprised the only positive finding on physical examination. X-ray examination was negative but an exploratory laparotomy was deemed expedient. Pre-operative diagnosis: deferred.

Operation was done November 5, 1916. A small, annular carcinoma was found in the transverse colon. It was resected and the bowel ends joined by lateral anastomosis. Pathological diagnosis: adenocarcinoma, grade II, with mucoid degeneration. The patient remained well for 4 years, then returned with numerous metastases to the liver and stomach from which he died a few months later.

It has been said by eminent surgeons that one of the justifications of laparotomy is to establish a diagnosis. This brings about many unnecessary operations but in a few cases such as Case 14, has made possible the diagnosis of a lesion of great significance. There was little in the clinical history to indicate a carcinoma. One should be suspicious, however, when pain of a dull aching character is more or less constant over a number of months. It is unusual for malignancy to recur in the bowel as late as 4 years, and naturally one suspects the presence of a new tumor, but since no autopsy was performed this point remained unsettled.

CASE 15. Path. No. 22763. White male, aged 41 years. A subjectively noticeable mass had been present in the right side for 6 weeks, causing moderate pain, dull and aching in character. In the upper right quadrant a hard nodular tender mass could be felt. Roentgenograms showed an obstruction in the first third of the transverse colon. Pre-operative diagnosis: malignancy of large bowel.

Operation was done January 30, 1918. The entire right half of the colon was resected together with the terminal ileum for a large mass arising from the transverse colon and involving the duodenum and ascending colon. Pathological diagnosis: medullary carcinoma without metastases. The patient was discharged from the hospital well but no ultimate result note was obtained.

Resection of the first half of the colon is sometimes a beneficial procedure. In this case the

tumor had involved the ascending colon and it was thought expedient to remove as much bowel as possible. The operation involves little more technical difficulty than simple resection, and frequently gives a much better result.

CASE 16. Path. No. 18672. White male, aged 47 years. For 2 months the patient had suffered from cramp-like pains in the abdomen and a sensation of fullness. He had been moderately constipated and vomited twice. Gaseous eructation and regurgitation which was at first acid in taste, changed to a fæcal character. He had lost 15 pounds. Peristalsic waves were seen in the upper abdomen, most prominent on the left side, where there was a superficial resistance in the abdominal wall. A gastro-intestinal series of roentgenograms indicated a pyloric obstruction with 24 hour retention. Pre-operative diagnosis: carcinoma of the pylorus.

Operation was done December 24, 1915. When the abdomen was opened the operator found a huge mass in the region of the gall bladder arising from the transverse colon and involving the stomach and gall bladder to such an extent that removal was out of the question. A palliative gastro-enterostomy was performed. Pathological diagnosis: carcinoma of the transverse colon; no specimen was obtained. The patient was discharged in 18 days improved, but died 4 months later with extension of the disease.

This patient showed symptoms of upper abdominal pathology which justified the diagnosis of carcinoma of the stomach. The presence of gall stones confused the picture but in spite of this a lesion in the lower tract was indicated by the characteristic fæcal vomiting.

CASE 17. Path. No. 17777. White female, aged 69 years. The patient had suffered intermittent attacks of pain and vomiting which were partially relieved by enemata for 6 months. The attacks increased in frequency and severity. She had lost some weight. The abdomen was found to be moderately distended and just to the left of the umbilicus was felt an indefinite slightly tender mass. Pre-operative diagnosis: malignancy of the bowel.

Operation was done May 20, 1914. On exploration a hard, annular tumor was found in the transverse colon. It was resected with the customary V-shaped piece of mesentery after ligation of the main branches of the colic vessels. The blind ends were anastomosed by the method of Bloodgood. Pathological diagnosis: adenocarcinoma, grade III, encircling the lumen and producing partial obstruction. One of the blind ends broke down 8 days after operation with a resulting fæcal fistula. This closed itself 5 weeks after operation. The patient was well when last heard from 5 years after operation.

Very few patients seek medical advice for constipation. It is nevertheless one of the most valuable and constant symptoms of gastro-intestinal tumors. Many individuals are constipated but very few over 40 years of age have a sudden and constant change of bowel habit without an underlying cause. This case illustrated again the advantages of "Bloodgood's thumb" anastomosis.

CASE 18. Path. No. 14512. White female, aged 64 years. This patient had suffered from occasional attacks of cramp-like pain for 3 months. She had lost 18 pounds in weight. When examined on entrance to the hospital the patient was evidently suffering from an acute obstruction. She was vomiting and in acute pain. The abdomen was extended and tympanitic. Pre operative diagnosis: acute intestinal obstruction.

Operation was done July 21, 1913. A colostomy was immediately performed to relieve the obstruction. At exploratory laparotomy 10 days later a small growth was found at the junction of the first and middle thirds of the transverse colon, causing a complete obstruction. The tumor was mobilized and removed after the method of Mikulicz, in two stages. Pathological diagnosis: adenocarcinoma, grade IV, surrounding the bowel and producing almost complete obstruction. The patient returned to the hospital 5 years later with a recurrence of the tumor in the psoas muscles. She died shortly after the second admission.

Carcinomata of the transverse colon do not customarily produce complete obstruction. When this occurs the underlying condition is apt to be overlooked and recognized only at operation. Two stages of operation are necessary in most cases, the preliminary colostomy for relief of obstruction preparatory to removal at the second. On the other hand certain operators feel that the patient suffers less from one operation and therefore remove the tumor when the abdomen is first opened.

CASE 19. Path. No. 12784. White male, aged 42 years. The patient had definite attacks of obstruction lasting 1 or 2 days at a time for a period of 2 weeks, increasing in severity and frequency. Six days before admission he became conscious of a mass in the middle of the abdomen. Constipation was marked and he suffered discomfort following the ingestion of solid food. He had lost an indefinite amount of weight. Examination disclosed a definite, hard, immovable mass on the left side of the iliac fossa. Other examinations were negative. Pre-operative diagnosis: malignancy of the bowel.

Operation was done May 15, 1912. The operator found on opening the abdomen a small annular tumor in the distal third of the transverse colon, with enlarged glands in the mesentery. The tumor was resected and the ends of the bowel anastomosed by the latéral method. Pathological diagnosis: scirrhous carcinoma surrounding and constricting the intestine; metastases present in the enlarged gland. The patient died 14 days after operation from bronchopneumonia.

The scirrhous type of tumor, that is to say the epithelial tumor characterized by a heavy fibrous reaction is most frequently responsible for constriction. This type of tumor is difficult to demonstrate by palpation but causes its symptoms early and metastasizes late. It is, therefore, one of the most favorable types to treat. The death from pneumonia in this case was not the fault of technique, and the autopsy showed a cleanly healed anastomosis.

CASE 20. Path. No. 12331. White male, aged 58 years. This patient suffered attacks of dyspepsia for a number of years. Three weeks preceding his admission to the hospital he had an acute exacerbation characterized by eructation and copious vomiting. Examination disclosed a

bulging mass in the right iliac fossa which was tense and at times showed peristalsic waves. This was tympanitic on percussion. X-ray examination revealed a dilated cæcum with obstruction at the first third of the transverse colon. Pre-operative diagnosis: malignancy of the transverse colon.

Operation was done January 11, 1912. On opening the abdomen the operator found the cæcum tremendously dilated, the result of an obstructing tumor mass in the transverse colon. He removed the right half of the colon *in toto* and performed an ileocolic anastomosis. Pathological diagnosis: adenocarcinoma, grade II, with mucoid degeneration. The patient died 8 days after the operation from generalized peritonitis.

When markedly distended the wall of the cæcum is thinned to such an extent that an anastomosis is hazardous, in view of the possible leakage. In Case 20 this fact led the operator to remove the entire right colon. In spite of this precaution, however, the patient died of generalized peritonitis.

Case 21. This patient had suffered increasingly severe attacks of pain in the lower abdomen for 6 months. She had lost 20 pounds in weight. For 2 weeks preceding admission to the hospital she had suspected a mass in the lower abdomen. She was admitted with an acute obstruction. The patient entered the hospital in agony. The abdomen was distended, tympanitic, and extremely tender. Pre-operative diagnosis: acute intestinal obstruction.

Operation was done August 5, 1929. The operator performed an exploratory laparotomy rather than a preliminary colostomy. He found in the left half of the colon a mass which had completely encircled the lumen causing almost complete obstruction. The tumor was resected with an adequate margin of normal bowel and a V-shaped piece of mesentery containing a few enlarged glands. The bowel ends were anastomosed with the end-to-end method. Pathological diagnosis: adenocarcinoma, grade II, of the constricting "napkin-ring" type; the glands were negative for carcinoma. The patient suffered partial obstruction following the operation for 2 years. At a second operation adhesions were released which had caused a partial obstruction at the site of the anastomosis. The patient is well at present 4 years after the first operation.

In this case the operator felt justified in doing the excision at the first operation. The fact that the patient did not recover entirely, does not discredit the method of procedure.

Case 22. Path. No. C-8974. White female, aged 66 years. This patient had noticed an upper abdominal mass for 5 years. For 2 years previous to admission she had been annoyed by a persistent diarrhœa. The mass had steadily increased in size but was not painful. She had lost 15 pounds in weight. Examination revealed a mass in the upper midline the size of an orange, which seemed to be adherent to the transverse colon and omentum. Pre-operative diagnosis: carcinoma of the transverse colon.

Operation was done June 3, 1928. On opening the abdomen the operator found a mass 12 centimeters in diameter surrounding the transverse colon in its middle portion but producing very little obstruction. This mass was resected with a few centimeters of normal bowel on each side and a section of the mesentery. The ends of the bowel were anastomosed by the end-to-end method. A portion of the ileum adherent to the tumor was also resected. Pathological diagnosis: adenocarcinoma, grade IV, transverse colon. The patient was discharged well and to date 4 years later has had no sign of recurrence.

This case again represents the type of patient who allows an abnormal mass to go unmolested for 5 years and consults a doctor only when symptoms occur which interfere with his daily activity. Modern medical teaching advocates early consultation for suspicious symptoms. The education of the laity leaves much to be desired and until patients learn to seek medical advice not only for annoying symptoms but also for any abnormal growth or condition, the ability of the physician to help them is lessened.

SUMMARY

Carcinomata are relatively rare in the transverse colon, only 7.3 per cent of all carcinomata of the colon being located in this region.

The clinical features differ little if any from those of carcinomata elsewhere in the bowel. Symptoms frequently simulate those of upper abdominal pathological conditions, such as gastric lesions or gall-bladder disease, and confusion of diagnosis is not rare. An achlorhydria is found in the majority of cases. Diagnosis is made by X-rays following both a barium meal and a barium enema. In cases in which the findings are doubtful, the series should be repeated.

It is surprising to find that tumors arising from the transverse colon involve the glandular system relatively infrequently. Metastases have a predilection for the liver. More common than metastases, however, is direct extension to the stomach and omentum, thereby causing the condition to be confused with carcinoma of the stomach. The majority of these tumors assume an annular constricting form and cause symptoms of partial obstruction.

Histologically, most of the tumors are of the adenocarcinoma type with secondary mucoid degeneration. This accounts for their tendency toward extension to adjacent structures with increased operative difficulty.

The optimum treatment consists of early radical resection, followed by anastomosis. The operator should give particular attention to the amount of bowel resected, the preservation of blood supply to the stumps, the prevention of tension on the anastomosis, and the method of anastomosis. Lateral anastomosis is to be preferred to the end-to-end method. The isoperistalsic or "thumb" method of anastomosis devised by Bloodgood is an advantageous procedure when sufficient bowel can be obtained without tension. This method

allows a possible rupture of the blind ends to take place outside the peritoneal cavity without causing peritonitis.

The results of treatment in 22 cases have not been gratifying. Five year cures have resulted in only 3 cases and cures of shorter duration in the same number. Postoperative deaths were 6, and deaths from inoperability or recurrence numbered 6.

The evaluation of early symptoms by the clinician with a resultant early diagnosis and careful attention to the above mentioned technical factors by the surgeon should enhance the patient's chances of recovery.

PUNCH BIOPSY IN TUMOR DIAGNOSIS

WILLIAM J. HOFFMAN, M.D., NEW YORK
Clinical Fellow in Cancer Research, Memorial Hospital

IN a previous communication,[1] the author described a new technique and instrument for obtaining biopsy specimens, and reported the results obtained with it in the diagnosis of twenty tumors. Since the publication of that paper the design of the instrument has been improved and an additional series of cases has been accumulated. This paper will describe the new punch, its advantages, technique of its use, methods of preparing the material obtained, and the results attained in the biopsy of 100 tumors.

The new punch consists essentially of three parts:

1. A tubular sheath fitted by a set screw to a forceps-type handle bearing a yoke which provides longitudinal movement to a specimen cutter operating within the sheath.

2. A specimen cutter, the lance-pointed tip of which serves as a trocar when the instrument is held in the closed position.

3. An insulated electrode the diameter and length of which are such that it may be introduced through the sheath and project beyond its end.

The sheath (Fig. 1) is a hollow metal cannula 12 centimeters long and 3 millimeters in diameter. Its distal end is ground to a circular cutting edge; its proximal end terminates in a tapered ferrule which is fitted to the handle by means of a set screw. The ferrule will accommodate the tip of a Luer syringe.

The specimen cutter (Fig. 1) is a cylindrical rod 15 centimeters long and 2.5 millimeters in diameter, fitting snugly within the sheath. Its proximal end terminates in a knurled knob and immediately distal to the knob is transfixed by a cross pin which engages in the yoke of the movable handle. By this means the specimen cutter can be extruded from or withdrawn into the sheath. The distal end of the cutter is ground to a sharp, lance point, and when the handles are closed, projects beyond the sheath to form a trocar. Immediately proximal to the lance point, the shaft is cut away so as to form a hook 5 millimeters long, the sharp edges of which fit snugly against the edge of the sheath when the cutter is withdrawn into it, thus exerting a shearing action on anything caught between the jaws of the cutter and the sharpened edge of the sheath. The forceps type handle consists of two limbs provided with finger holes and so pivoted that approximation or separation of the handles causes retraction or extrusion of the specimen cutter.

The electrode (Fig. 1) is a slender conductor 18 centimeters long and 2 millimeters in diameter, capable of being introduced through the interior of the sheath and of being extended about 1.5 centimeters beyond its edge. It is insulated over its whole surface except at its distal extremity where it terminates in a hemispherical knob 2 millimeters in diameter. The proximal end is fitted with a standard insulated split connector designed to receive the connecting cable tip of a source of coagulating (surgical diathermy) current.

TECHNIQUE OF PUNCH BIOPSY

The skin and tissues overlying the suspected tumor are infiltrated with novocain and some of the anæsthetic is injected deeply along the proposed path of the instrument, puncture of the tumor being avoided, however. A 3 millimeter stab wound is then made through the skin with a sharp pointed bistoury. With the punch closed so that the cutter is withdrawn into the sheath, only the sharp lance point being left exposed, the instrument is introduced through the puncture

[1] Hoffman, William J. New technique and instrument for obtaining biopsy specimens. Am. J. Cancer, 1931, xv, 212.

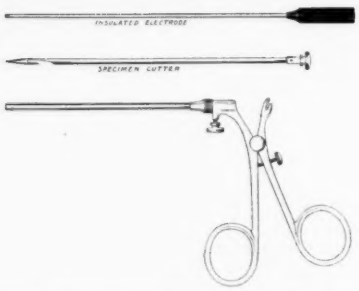

Fig. 1. The three parts of the biopsy punch: insulated electrode, specimen cutter, sheath fitted to forceps-type handle.

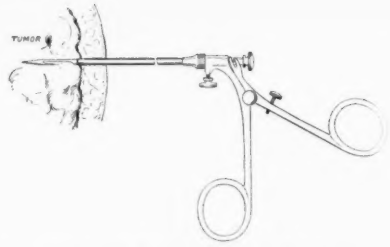

Fig. 2. The punch introduced through puncture wound and the cutter extruded into the tumor, ready to cut specimen.

wound and thrust through the subcutaneous tissue into the tumor. When the point is felt within the tumor at the site selected for biopsy, pressure is made on the knob of the specimen cutter and the handles allowed to open. This causes the exposure of the hook shaped cutter. Gentle outward traction causes the hook to imbed itself into the tumor. The handles are then closed, thus causing the cutter to be withdrawn into the sheath and cleanly cutting away the tissue caught between the cutter and the sheath. The cutter is then completely withdrawn with its contained specimen through the inside of the sheath without contaminating the intervening normal tissues, leaving the sheath in position. If additional tissue is desired, the cutter is reintroduced and as much tissue as may be required is removed through the same puncture without an additional breach being made in the tumor. The insulated electrode, connected to a source of coagulating current, is then introduced through the sheath so that the tip of the electrode occupies the point on the tumor from which the specimen was cut away. A current of about 250 milliamperes is switched on, the electrode is held in contact with the area for about 2 seconds, and then slowly withdrawn with the punch so that a thin film of coagulation is produced along the needle track.

Biopsy of cyst wall. If, when the punch is introduced, there is a sudden loss of resistance and the suspicion verified that the tumor is a cyst, the cutter is extruded within the cyst cavity and then drawn outward slightly so that the hook is imbedded into the proximal wall. Closure of the handles causes the cutter to punch out a portion of the cyst wall, and the specimen thus obtained may be drawn out through the sheath in the usual way. The cyst contents may be allowed to drain out through the sheath. If the fluid is too viscous to flow readily, the handle of the punch should be disconnected so as to permit the attachment of a syringe to the proximal end of the sheath and the aspiration of the contained material. If desired, opaque media may be introduced through the sheath for radiographic determination of the relations of the cyst to the surrounding structures.

Biopsy of prostate gland. Biopsy of the prostate gland is performed in a manner similar to that already described for other localities. The punch is introduced through the perineum at a point about 1 centimeter lateral to the midline, and the point of the punch is thrust forward into the selected area of the prostate, being guided by a palpating finger in the rectum.

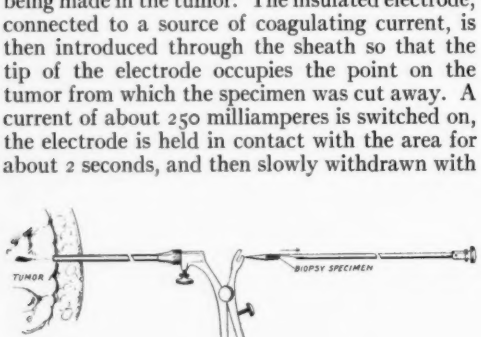

Fig. 3. Specimen is withdrawn through the sheath without contaminating the normal intervening tissues, leaving the sheath in place.

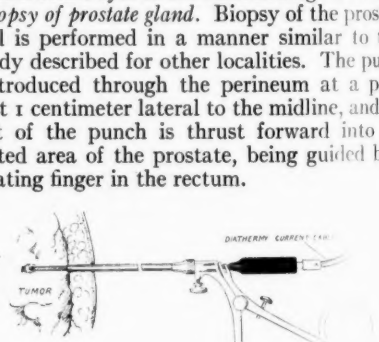

Fig. 4. The electrode has been introduced through the sheath and is shown coagulating the opening in the tumor and the needle track.

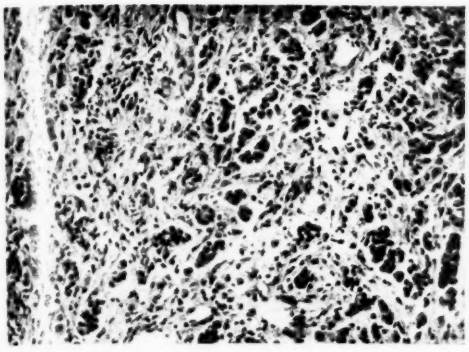

Fig. 5. Case 82. E. L. Punch biopsy of breast tumor. Paraffin section. Infiltrating duct carcinoma.

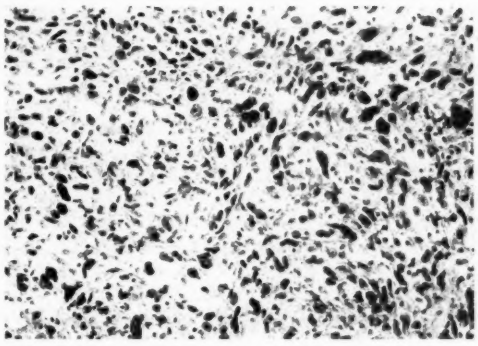

Fig. 6. Case 100. E. B. Punch biopsy of tumor of scapula. Paraffin section. Large spindle and giant cell osteogenic sarcoma.

Preparation of the specimen. The piece of tissue obtained by the punch measures 5 by 2.5 by 2.5 millimeters and is large enough for an immediate smear, frozen section, or paraffin preparation. If the tissue is soft and cellular a smear may be made by crushing a small portion between two glass slides, or by touching the specimen to several areas on a glass slide previously warmed over a flame. This will cause the specimen to adhere and thus detach some cells. These smears when stained by hæmatoxylin and eosin afford a finished preparation in 6 to 8 minutes.

The solid piece of tissue is placed in 10 per cent formalin and carried through the regular stages of fixation to be made into permanent paraffin block preparations. Four or five sections are usually cut from these blocks and mounted on a single slide. The finished result is a section of an actual piece of undistorted tissue from which a pathological diagnosis can usually be made. If greater haste is required, a quick paraffin section can be prepared in about 3 hours.

In this series of 100 tumors, the biopsy specimens, as a general rule, were prepared as immediate smears and paraffin sections. The advantage of the former is that a diagnosis may possibly be made in a few minutes; the disadvantage is that because the characteristic structure is lost the diagnosis of a smear must rest on the abnormal morphology of some clumps of cells. The information gained is, therefore, often limited. The paraffin sections require longer to prepare but afford an excellent final result which, except for size, is similar to the sections ordinarily encountered by pathologists. Because they present a section of undistorted tissue their diagnosis does not demand the special experience required in the interpretation of smears. It naturally follows also that more information can be gained from the section than from the smear. For instance, one can determine not only whether or not a certain tumor is malignant, but often also its pathological classification and whether or not it is likely to prove radiosensitive.

CLINICAL APPLICATIONS

The biopsy punch has been employed at the Memorial Hospital in the diagnosis of tumors located within the body beneath normal overlying structures. It has not been used within the abdominal or thoracic cavity, and only with caution in the neighborhood of important vessels and nerves. By this means it has been possible:

1. To diagnose obscure tumors entirely lacking pathognomonic features which would have indicated their character;

2. To obtain definite knowledge of the pathological type of a disputed tumor and thus decide

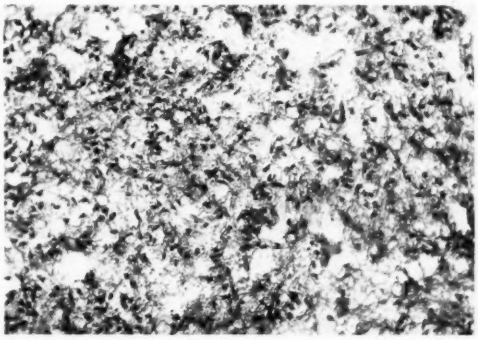

Fig. 7. Case 99. Punch biopsy of subcutaneous tumor of thigh. Paraffin section. Myxolipoma with low grade malignant characters, i.e., liposarcoma.

upon the treatment (whether surgery, irradiation, or both);

3. To secure adequate histological proof of the nature of inoperable tumors destined to be treated by irradiation;

4. To determine the ultimate effect of irradiation on tumors apparently successfully treated by that method several years previously.

CLINICAL RESULTS

In a series of 100 punch biopsies done during the past 2 years at Memorial Hospital, there have been no accidents. Hæmorrhage or infection have never occurred. Trauma is negligible since only a single puncture is made. The danger of local or general dissemination is probably slight; the coagulation of the puncture wound in the tumor and of the needle track attempts to eliminate this danger.

This series of 100 punch biopsies included tumors of breast, prostate, bone, cervical, axillary and inguinal nodes, as well as subsurface tumors generally. The consistence and structure ranged from that of a simple cyst to that of an osteogenic sarcoma of bone. In every case tissue was obtained on the first attempt at biopsy. From the specimens obtained from these 100 tumors, 93 positive diagnoses were made (93 per cent). In 7 instances the material obtained by the punch failed to reveal any evidence of neoplastic disease, although there was evidence in 4 of these cases to warrant that clinical diagnosis. In the 3 remaining cases (33, 35, and 37), there was no palpable tumor present and the only evidence of abnormality was an increased consistence of the breast. These cases are here listed as failures although it is doubtful that any malignant tumor is present. Thirty-six of these 100 tumors have been removed surgically and the whole specimens submitted to pathological study. In 34 of these cases the diagnosis made after examination of the whole specimen agreed with that made from the specimen obtained with the punch. The 2 exceptions were Cases 9 and 32. In both these instances the punch had not been introduced into the tumor and only normal tissue had been obtained. In no case, on the other hand, has a positive diagnosis of malignancy made from the biopsy punch material been contradicted by the diagnosis made after examination of the whole excised tumor.

Seventeen of these tumors had been treated by heavy doses of interstitial irradiation from 1 to 7 years previous to punch biopsy, so that they were reduced to hard, shrunken, and, in some instances, calcified nodules of scar tissue. In 12 instances, strands of carcinoma cells were demonstrated among the dense whorls of radiation fibrosis. In the 5 remaining cases, no cancer cells could be demonstrated. In these latter 5 cases the cancer presumably has been destroyed. In each, the persistent tumor was reduced to a small nodule and there was no clinical evidence of activity. They are, therefore, listed among the successful biopsies since it is a fairly reasonable assumption that the cancer has been eradicated.

ADVANTAGES

Among the advantages of this instrument and technique are these:

1. By means of this instrument and technique of biopsy, early diagnosis may be obtained at a time when pathognomonic clinical features are not yet developed.

2. It is a minor procedure done under local anæsthesia in the physician's office at the time of the first examination. Most patients who refuse the suggestion of an operative biopsy, consent readily to a punch biopsy.

3. A solid piece of unchanged tissue is obtained.

4. The piece of tissue is large enough to exhibit the characteristic structure of the portion of the tumor from which it was removed, and to furnish material for immediate smear, frozen section, or paraffin preparation.

5. The tumor is punctured but once, although additional pieces of tissue may be obtained through the original puncture wound, if desired.

6. The cutting action is positive; the tissue is cleanly cut away; the specimen is not crushed or coagulated. The normal structural relations, in most instances, are preserved.

7. It is successful in a wide variety of material, whether fluid, semi-fluid, caseous, soft cellular, densely fibrous, or osteoid in character (bone tumors which have eroded the cortex).

8. By means of the punch a specimen may easily be obtained from the wall of a cyst, and by means of a syringe fitted to the sheath its contents may be evacuated or opaque media injected.

9. The opening in the tumor and the needle track are coagulated before withdrawal of the punch, thus rendering less likely the dissemination of the disease.

10. The punch in 100 cases has never failed to obtain a specimen from any tissue into which it has beenin troduced. Successful diagnoses were made from material obtained in 93 per cent of cases.

SUMMARY

A new technique and biopsy punch are described and illustrated. By means of this punch

and technique an actual undistorted piece of a suspected tumor is obtained through a small puncture wound and removed through a sheath without contaminating the intervening normal tissues. The opening in the tumor and the needle tract are coagulated by an insulated electrode connected to a source of high frequency (surgical diathermy) current as the instrument is withdrawn.

The use of the punch and the methods of preparing the specimen are described. Biopsies by this method have been performed on 100 patients at the Memorial Hospital, this group including a wide variety of tumors and many of dense fibrous structure.

An actual piece of tissue was obtained in each case on the first attempt. From these specimens paraffin sections and smears were prepared. Successful diagnoses were made in 93 instances (93 per cent). Thirty-six of these tumors were later removed surgically and the punch biopsy diagnoses were checked by comparison with the pathological diagnosis made after examination of the whole specimen. In all but 2 cases the final pathological diagnosis agreed with the diagnosis made from the punch biopsy specimen. The exceptions were cases in which the punch had not been introduced into the tumor and only normal tissue had been obtained. The accuracy of diagnosis in these checked cases was thus about 94 per cent.

The action of the instrument is safe, simple, and positive. In the whole series there has not been an instance of fungation, infection, or hæmorrhage. The danger of local or general dissemination appears to be slight; trauma is negligible; the coagulation of the puncture wound in the tumor and of the needle track is an attempt to eliminate this danger.

This article was awarded Certificate of Honor, Class II, by the American Medical Association at the Philadelphia Session, June, 1931.

The author gratefully acknowledges the co-operation of Mr. Reinhold Wappler of the American Cystoscope Makers, Inc., whose technical knowledge and mechanical skill were of material assistance in developing this instrument.

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APRIL, 1933

GASTRIC ULCER IN ITS RELATION TO CARCINOMA OF THE STOMACH

NO more illuminating study of cancer of the stomach has been published in recent years than the paper by Alvarez, dealing with 41 physicians who were treated for it at the Mayo Clinic. Physicians are supposedly aware of the devious ways of this treacherous disease, are supposedly on the alert for its recognition, are supposedly convinced that in the battle against it surgical treatment and prompt surgical treatment is the only hope of salvation. But what did this group of physicians do? Did they promptly suspect cancer when they developed symptoms of gastric discomfort, of prolonged and progressive digestive disturbance, of actual obstruction? Did they promptly submit to radiological study? Did they promptly demand surgical exploration? The great majority of them did none of these things. The great majority of these men and women who should have known better either ignored their symptoms entirely or else permitted themselves to be treated for indefinite periods of time by medical measures, apparently without suspecting that they had set their feet on the way that leads inexorably to death. Small wonder, in the face of this record, that laymen procrastinate as they do: when the shepherd strays, one cannot expect the sheep not to wander from the path.

Particularly noteworthy in this study just as he is noteworthy in any similar study, is one special type of patient. He tells a long story of previous indigestion, which has perhaps responded well in the past to medical treatment, but which now remains obdurate to it. Or he suddenly exhibits an exacerbation of symptoms or a change in symptoms. That was the sort of history that was given by 21 of the 41 patients Alvarez studied, and it is the sort of history that immediately introduces either the possibility of a previous ulcer or the absolute certainty of one. The relation of gastric ulcer to gastric carcinoma is a question upon which authorities of equal eminence hold opinions that are diametrically opposite, but Alvarez is perfectly correct when he says that the man who can ignore such facts as these has a mind that is impervious to evidence of any kind.

The origin of cancer is an academic consideration, as is the question of the exact percentage of gastric ulcers which turn into cancer, or the number of cases of cancer which are superimposed upon ulcers. The microscopic, radiological, and clinical criteria which must be invoked to solve the problem fade into insignificance beside the fact that some cancers apparently develop from ulcers, that some ulcers apparently develop into cancers, and that some supposed ulcers are undoubtedly cancers from their inception. The cr[illegible] of the

problem, therefore, is whether or not the prolonged medical treatment of gastric ulcers is safe. Such treatment, as Alvarez points out, is always based upon the fallacious assumption that the differentiation of gastric ulceration from gastric malignancy is possible by clinical and radiological methods, whereas repeated studies have shown that this is not only not possible but also that it is not even approximately accurate.

A guess, which in some 25 or 30 per cent of all cases is the best that the most experienced clinician and radiologist can offer, is a poor peg, as Lord Moynihan says, upon which to hang a man's life. And make no mistake, it is a life that is in the balance. The medical treatment of gastric ulcer may be relatively safe, even if it does not relieve the patient, but the medical treatment of gastric cancer is equivalent to manslaughter or suicide, from whichever point of view you happen to be regarding it. Gastric ulcer and gastric malignancy must be distinguished positively, not probably, before the medical treatment of the supposed ulcer is undertaken. The surgeon must be absolutely certain that he is dealing with an ulcer before he withholds surgery, regardless of how unlikely or how uncommon he personally feels the transition to malignancy to be.

The only safe rule is to regard as cancer any indigestion, with or without other symptoms, which appears after middle life in a previously well person, to regard as cancer any acute digestive disturbances in this period which are superimposed upon chronic digestive disturbances and which do not respond promptly to routine measures; to regard as cancer or as highly suspicious of it vague general symptoms, even though associated gastric disturbances are lacking; to continue to regard as cancer any of these clinical syndromes until it is proved beyond a shadow of doubt that it is not cancer; and to resort without delay to exploratory laparotomy if the diagnosis cannot be made otherwise. The suspicion that cancer exists is the one thing that matters; in malignant disease the certainty of diagnosis is frequently also the certainty of death. "The salvation of human life," says Lord Moynihan, "is a greater thing than the establishment of a convincing, irrefutable clinical diagnosis," and Arthur Curtis remarks in another connection that "it is better to have a less accurate diagnosis and a more favorable prognosis." Operation on suspicion is justified in this disease, in which one can scarcely tell what a day will bring forth, or at what moment an operable lesion may become an inoperable one. Accurate diagnosis is a desideratum, but in the absence of incontrovertible negative findings, or in the presence of doubtful positive findings, the surgeon is entirely justified in exploring without hesitation every person in middle life or before middle life who exhibits a dyspepsia which does not respond promptly and permanently to established methods of treatment: cancerous indigestion has no hallmarks, while it is still amenable to cure, to distinguish it from indigestion of other origins. A properly performed exploratory incision was never responsible for a fatality, and the multitudes cannot be counted whom it has saved from death. URBAN MAES.

THE TRAINING OF THE SURGICAL NURSE

THE prime objective of the nursing profession, as well as that of the medical profession and hospitals, is the prevention and cure of disease. The duty of the hospital to train nurses is secondary to their obligation to give the best care to sick patients. The time was when the best interests of surgically sick patients were most efficiently guarded by having every pupil nurse receive

some practical training in operating-room procedure, including the very particular and technical work of "handling instruments" at operations. This covered the period of antiseptic surgery and the early days of aseptic surgery, when the facilities of the modern hospital had not yet been made accessible to all communities by the modern road and ambulance. In those days, fortunately past, any nurse might have been called upon to prepare for a major operation in any home. Today there is rarely a call for such service. The passing of this need has not seen the nurse training schools alive to the change.

The nursing schools are putting each pupil through the mill of operating-room service when today the best interests of the patient can be advanced very materially if the patient be not made the means of practice and training. No medical school trains its students in technical surgery. These students receive their technical surgical training in graduate courses as internes and as assistants to trained surgeons. The surgical clinic of today that is not associated with a training school, or the one that uses graduate operating-room nurses, all other things being equal, is giving the best service to the patient and enabling the doctor to do his best by his patient.

The qualifications of a good surgical nurse assistant are exact, rigid, and specific. A few of these are: physical and nervous stability, evenness of temper, control of emotions, ability to think and to act quickly in an emergency, unusual capacity for the details and minutiæ of preparation for an operation, dependability which is the result of uniformity of procedure, and yet an adaptability to the infinite variations that make each similar operation different from every other one. She must have that peculiar quality of intuition that permits the *rare* assistant to be just a step ahead of the operator, to anticipate his needs before they are expressed. In a class of sixty girls, evenly selected girls, not over 10 per cent show any large proportion of these qualifications. Technical work requires specialization.

The Class A hospital of today, backed by the American College of Surgeons and the American Medical Association is demanding the highest qualifications of those surgeons permitted the privilege of utilizing its operating rooms. Such a hospital states that it owes a duty to the public at large and so must assure the public that only an efficiently trained surgeon may use its facilities. This being true, the same hospital should be allowed to furnish equally efficient technically trained nurses. This these very excellent hospitals do not do, for the rules governing trained, registered nurses, require that every nurse, no matter what her personal characteristics, be put through a six, eight, or ten weeks' operating-room course and made to "assist" with at least twenty-five operations. The medical college does not try to make every student a surgeon. They know that the surgeon must be born as well as made. The surgeon selects his specialty because of a love for surgery. The December, 1932, examinations for nurse registration in Ohio specifically asked: "For how many operations have you been the sterile nurse? Majors? Minors?" The most perfectly adapted nurse for this technical work cannot hope, by any stretch of the imagination, to acquire proficiency in the time allotted. For a large proportion it represents time lost and lost at the expense of the hospital, the doctor, the nurse teacher, and above all, the patient.

How can this situation be corrected? Just two adjustments are necessary. First, change the regulations to make it unnecessary for the pupil nurse to "handle" instruments for operations. Second, require that the "sterile" nurse

who "handles" the instruments at the operation be a graduate nurse. She may have an undergraduate "sterile" assistant.

What will be accomplished by these changes? Many nurses will not be given a responsibility for which they are unfitted. Numberless hours of futile effort will be saved on the part of nurse supervisors and doctors. The placing of the student as "sterile" assistant to the "sterile" graduate operating nurse will give the intelligent pupil all she needs of knowledge of surgical asepsis and technique and permit her to obtain this training at an early period in the school schedule, to the benefit of her subsequent training. (Many advanced thinkers on the subject of nurse training feel the operating-room experience should come early in the three years' course.) Valuable time will be saved during each operation, and while a few minutes more or less do not appreciably change the result of the average operation, these minutes saved may mean a life saved in the bad-risk and emergency case. It means the assurance of a more perfect technique to the end that complications may be eliminated. It means the surgeon's attention can be centered on the actual operation technique, so that he will not have to divert his attention from the field of operation to direct a "green" nurse assistant. It means less wear and tear on the surgeon, which in turn means better service to the patient.

Team work has become essential to good surgical work. The anæsthetist, assistant, nurses, and surgeon must work together. One new "cog-wheel" in the engine or one "green" horse in the team, slows up the work and makes it less efficient. Who suffers? The patient. It, therefore, behooves the medical profession, hospitals, and the nurses themselves, to see that the rules regulating these affairs are arranged to give the patient the best service possible. DUDLEY W. PALMER.

MEMOIRS

GEORGE DAVID STEWART

DECEMBER 28, 1862—MARCH 9, 1933

Thou Power Supreme, whose mighty scheme
These woes of mine fulfill,
Here, firm, I rest,—they must be best
Because they are Thy will.
Robert Burns.

THE officers, regents, and administrators of the American College of Surgeons mourn the loss of a distinguished founder and a past president, George David Stewart.

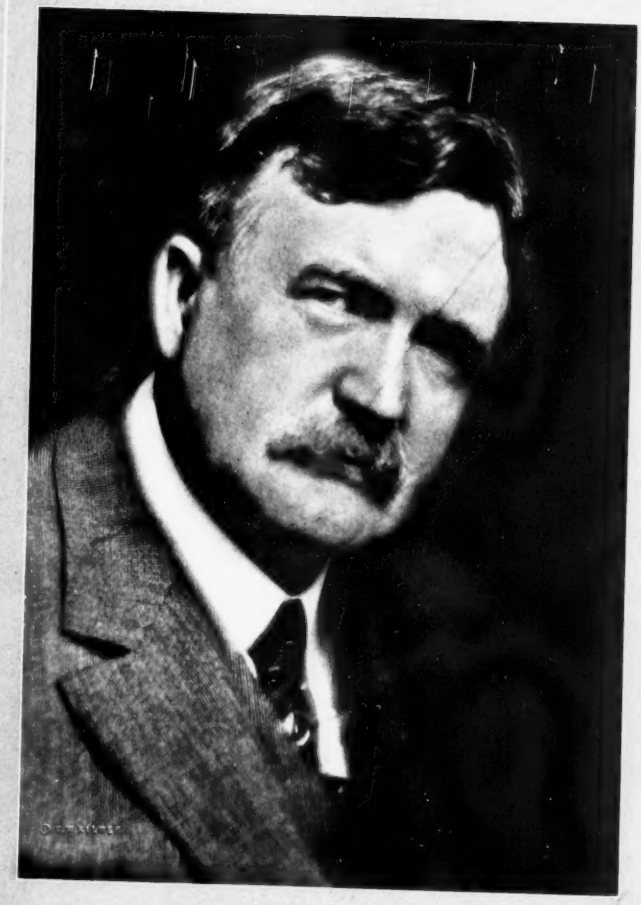
He was a great man, a great American, a great surgeon; and one of the most beloved members of the profession. Among his outstanding qualities were his strong character, his human heart, his love for his fellow man, his unfailing friendship and loyalty, his honesty of thought, his fearlessness, his tireless energy, his fund of humor, and his over-powering personality.

We shall miss his inspiring presence at the meetings of the College and of the Clinical Congress, his happy companionship, and his courageous support of those principles which were on the side of right.

On several occasions I heard from his lips the following words from Havelock Ellis: "The present is in every age merely the point at which the past and future meet. . . . There is never a moment when the new dawn is not somewhere breaking over the earth and never a moment when the sunset ceases to die; we should greet the new dawn serenely, not hastening toward it with undue speed nor yet leaving without regret the dying light that was once dawn."

His belief that "civilization must move, our profession must move; both are dynamic, not static; and change is life" was best exemplified by his interest in the younger men of the profession to whom his very life was a constant inspiration, and in whose accomplishments lay his greatest pride. It is only fitting, therefore, to append some notes on phases of Doctor Stewart's life by one of his "boys" who was associated with him for twenty-five years.

FRANKLIN H. MARTIN, M.D.



Geo. David Stewart

GEORGE DAVID STEWART was born in Upper Malagash, Cumberland County, Nova Scotia, on the shores of Northumberland Straits, where the climate is ten months of winter and two months of late fall; a lovely place with magnificent views in the summer—when there is a summer.

The teachers in the country school which he attended were not educated; but one, who influenced his life in his tenderest years, knew how to sing Methodist hymns, and how to read and write. His early education was fatuous, and depended largely on the library of his grandfather—a library which consisted of the Bible, Bunyan's *Pilgrim's Progress*, Jeremy Taylor's *Holy Living and Dying*, Boston's *Fourfold State*, Baxter's *Call to the Unconverted* and *Saints' Everlasting Rest*, and the poems and songs of Robert Burns. The Bible he was compelled to read; Robert Burns he read from choice. Hence, he had a fine collection of the latter's poems tucked away in his brain for ready reference.

At the age of fourteen, he ran away to sea. The schooner on which he shipped was a slow one, and sailed steadily for six weeks. This sufficed to prove that seafaring was not his metier. Then by luck, on his return home, a very good teacher came along, and one year's instruction under that teacher enabled him to teach himself. He taught a country school, later graduated from the Normal School, Truro, and St. Francis Xavier College, Antigonish, Nova Scotia, and served as the principal of a village high school. He just escaped being a preacher.

Doctor Stewart graduated from Bellevue Hospital Medical College in 1889. After his internship of one year at Bellevue Hospital he was appointed preceptor in demonstrative anatomy, and later professor of anatomy. It was his good fortune to serve at Bellevue under Joseph D. Bryant, Frederic S. Dennis, and the elder Thayer. In 1914 he succeeded Dr. Bryant as professor of surgery, University and Bellevue Hospital Medical College, and it was here that he accomplished his greatest work. His teaching clinic was unexcelled.

As a lecturer he had few equals. At the conclusion of each lecture he insisted that the notes should be destroyed. In this way, by constant re-preparation, he kept his mind virile. In recognition of his achievements, his friend, the late George F. Baker, gave a million dollars to found the George David Stewart Endowment for Surgery.

He disliked writing articles on surgery. To use his words: "There is more loose motion in the contributions to medical science, particularly surgery, than in anything else except in a wooden doll or a marionette."

To estimate Doctor Stewart from his published literary contributions to surgery would be unfair and unjust. His impress on American surgery can be properly evaluated only by those who have enjoyed his care and his skill, and those thousands of young men who have felt the influence of his personality and of his character as a teacher and as a man.

ARTHUR M. WRIGHT, M.D.

EARLY AMERICAN MEDICAL SCHOOLS

THE EARLY HISTORY OF THE FIRST MEDICAL SCHOOL IN THE COLONIES—THE UNIVERSITY OF PENNSYLVANIA

I. S. RAVDIN, B.S., M.D., PHILADELPHIA

WHEN William Penn founded his colony in Pennsylvania in 1682, he undoubtedly considered the medical needs of the colony for he brought with him on the *Welcome*, Thomas Wynne. Griffith Owen and other men trained for the medical profession arrived during the autumn and winter of the same year. In 1711 John Kearsley arrived and in 1717 Thomas Graeme. These men and others who came during that period acted as the teachers of their art and as the preceptors of the rising generation. Their successors were for the most part natives of this country. Of these, Thomas Cadwallader, William Shippen, Sr., Thomas Bond, Phineas Bond, John Redman, John Kearsley, Jr., Lloyd Zachary, Cadwallader Evans, and John Bard played important parts in the early medical activities of the colony.

The older men fired the imagination of their apprentices with the advantages to be obtained by subsequent training at Edinburgh, London, Paris, or Leyden, and most of the younger men added to their preparation by studying at one of these places.

"In the settling of new countries, the first care of the planters must be to provide and secure the necessaries of life. . . . Agriculture and mechanical arts, were of the most importance; the culture of the minds by the finer arts and sciences, was necessarily postponed to times of more wealth and leisure." Thus it was that on the 24th of August, 1749, Benjamin Franklin announced the prospectus of his scheme for the higher education of the youth of the colony and from it developed the University of later years.

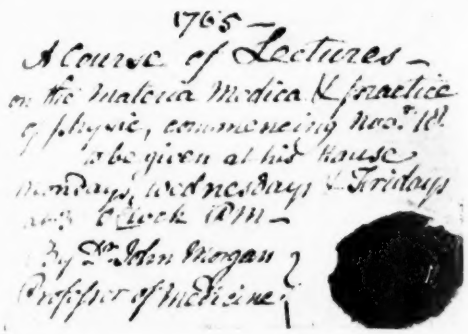
Two years later Thomas Bond sought Franklin's assistance in the building of a general hospital for the sick and injured. On the 23rd of January, 1751 "Sundry Inhabitants" of the Province of Pennsylvania had petitioned the Assembly for the establishment of a permanent, public hospital. While Franklin and Bond were busy arranging for the beginning of the Academy to train the mind, they also found time to plan the institution which was to provide the means for the founding of the Pennsylvania Hospital. The hospital was first located in a house on Market Street near Sixth, but on the 28th of May 1755, the corner stone of what is now known as the East Wing was laid on the present site. Franklin's inscription on the corner stone was as follows:

IN THE YEAR OF CHRIST
MDCCLV
GEORGE THE SECOND HAPPILY REIGNING
(FOR HE SOUGHT THE HAPPINESS OF HIS PEOPLE)
PHILADELPHIA FLOURISHING
(FOR ITS INHABITANTS WERE PUBLICK SPIRITED)
THIS BUILDING
BY THE BOUNTY OF THE GOVERNMENT,
AND OF MANY PRIVATE PERSONS
WAS PIOUSLY FOUNDED
FOR THE RELIEF OF THE SICK AND MISERABLE:
MAY THE GOD OF MERCIES
BLESS THE UNDERTAKING.

It was thus that the Pennsylvania Hospital and University were born of the same parentage and most of the professors in the earlier years of the Medical School were on the staff of the Hospital.

Thomas Cadwallader, who had studied anatomy in London under the celebrated Cheselden, settled in Philadelphia and gave demonstrations to the physicians of the locality. Since Cadwallader established himself in Philadelphia before 1751 he was probably the first to give anatomical lectures in America. There was as yet no School of Medicine and sixteen years were to elapse before the College and Academy could boast of one.

John Morgan, who had pursued his medical studies under John Redman, went to Europe in 1760. For two years he attended the lectures at the University of Edinburgh, from which institution he received his degree in 1763. Before going to Edinburgh he had attended William Hunter's lectures in London, and subsequent to his study in Edinburgh he went to Paris, Holland, and Italy.


1765
A Course of Lectures
on the Materia Medica & practice
of physic, commencing Nov.r 18.
to be given at his house
Mondays, Wednesdays & Fridays
at 5 o'clock PM
By Dr. John Morgan
Professor of Medicine

Front of first admission card to John Morgan's lectures. A playing card was used.

Department of medicine. East side of Fifth street, between Library and Walnut Streets, 1765 to 1802. Building known as Surgeons' Hall.

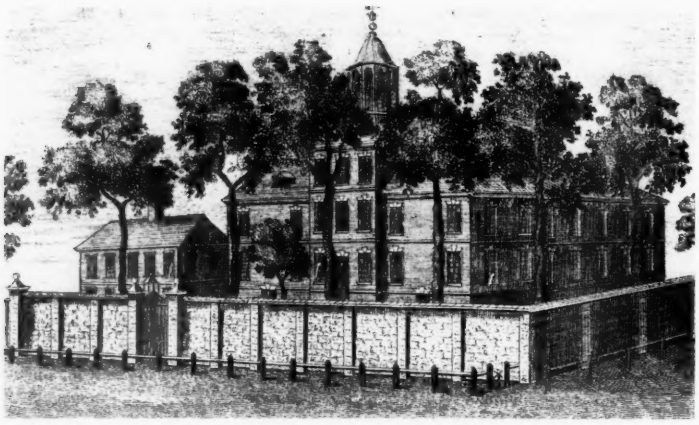
While in London in November, 1764, he wrote to Dr. Cullen in Edinburgh: "My scheme of instituting lectures you will hereafter know more of. It is not prudent to broach designs prematurely, and mine are not yet fully ripe for execution." He had discussed his plans with the younger Shippen while they were together in Edinburgh. Shippen had returned to the Province in May, 1762, and on November 25 of that year he announced in the *Pennsylvania Gazette* "Dr. Shippen's Anatomical Lectures will begin to-morrow evening, at six o'clock, at his father's house in Fourth Street. Tickets for the course to be had of the Doctor, at five Pistoles each, and any gentlemen who incline to see the subject prepared for the lectures, and learn the art of Dissecting, Injections, etc., are to pay five Pistoles more." In later years Wistar, who became one of the great anatomists, remarked "Such was the origin of our medical school." These lectures indeed proved to be the beginning of the broader plan of Morgan, which was to found the Medical School of the College and Academy of Philadelphia.

John Fothergill of London had always evinced an interest in the medical affairs of the Province. The Pennsylvania Hospital having been erected, he took it for granted that students would resort to it, and well he knew the difficulties that would beset them in the acquisition of a knowledge of anatomy. To remedy this defect Fothergill employed Rimsdyck to execute crayon paintings of the human anatomy.

Shortly after Shippen returned he advised the managers of the Hospital that Fothergill had sent seven cases of anatomical drawings. In a letter to James Pemberton, Fothergill had written: "and that the means of procuring subjects with you are not easy, some pretty accurate anatomical drawings about half as big as the life, have fallen into my hands, which I propose to send to your hospital. . . . I have recommended it to Dr. Shippen to give a course of Anatomical Lectures. . . . He is well qualified for the subject, and will soon be followed by an able assistant, Dr. Morgan, both of whom, I apprehend, will not only be useful to the Province in their employments, but if suitably countenanced by the Legislature will be able to erect a School of Physic amongst you, that will draw students from various parts of America and the West Indies. . . ."

Morgan arrived in Philadelphia early in 1765 and at a special meeting of the Trustees of the College and Academy, called for on the 3rd of May, 1765, which was attended by Thomas and Phineas Bond, Cadwallader and Redman, Morgan presented his plan. He brought with him a letter from the Proprietory, Thomas Penn, which was indeed laudatory. "Dr. Morgan has laid before me a proposal for introducing new professorships in the Academy. . . . We are acquainted with what is proposed to be taught . . . and desire that he may be well received, and what he has to offer be taken, with all becoming Respect and Expedition, into your most serious Consideration."

After considering the matter ". . . . The Trustees entertaining a high sense of Dr. Morgan's Abilities, and the Honors paid to him by different Learned Bodies and Societies in Europe, they unanimously appointed him Professor of the Theory and Practice of Physick in this College." On May 30 and 31 of the same year Morgan gave his inaugural oration "A Discourse upon the



The first wing of the Pennsylvania hospital.

Institution of Medical Schools in America." Morgan was the first physician in Philadelphia to restrict himself to simply prescribing for the sick. "Can any man, the least acquainted with the nature of that arduous task, once imagine it possible for me to acquit myself in that station in an honorable or useful manner, and yet be engaged in a continued round of practice in surgery and pharmacy as well as physic?" On September 23 of the same year, Shippen was appointed to the professorship of anatomy and surgery, and on September 26 the following announcement appeared in the Pennsylvania Gazette "As the necessity of cultivating medical Knowledge in America is allowed by all, it is with pleasure we inform the public that a Course of Lectures on two of the most important branches of that useful science, viz., Anatomy and Materia Medica will be delivered this winter in Philadelphia. . . . In order to render these courses the more extensively useful, we intend to introduce into them as much of the Theory and Practice of Physic, of Pharmacy, Chemistry and Surgery as can be conveniently admitted.

"From all this, together with an attendance on the practice of the physicians and surgeons of the Pennsylvania Hospital, the students will be able to prosecute their studies with such advantage as will qualify them to practice hereafter with more satisfaction to themselves and benefit to the community." It was signed by Morgan and Shippen.

The first class of students was enrolled in the fall of 1765, and of these ten were graduated with the Degree of Bachelor of Physic in 1768, "the birthday of medical honors in America." The question as to whether the College of Philadelphia or King's College in New York has the honor of priority in the awarding of medical degrees in this country may now be answered. The degrees of Bachelor of Medicine conferred June 21, 1768, by the College of Philadelphia, were the first medical degrees conferred by an institution in the colonies. King's College conferred the same degree for the first time in 1769 and the degree of Doctor of Medicine in 1770. From this it appears that the claim of priority in conferring degrees in medicine must be awarded to the College of Philadelphia, while the precedence in conferring the Doctorate must be given to New York. Morgan and Shippen constituted the major Faculty until January 1768 when Adam Kuhn was made professor of botany and materia medica. Kuhn, also, had received a part of his medical training in Edinburgh.

Thus, the first medical school in North America was in reality an offspring of the most brilliant school in Europe at that time. The professors had unavoidably acquired an affection and preference for the Scottish school's type of instruction, and for many years the major portion of its professorial faculty received some of their training within the walls of Edinburgh. The University has continued to feel a very close connection to its patron over the seas, and the iron grill over the present entrance contains the thistle. The first medical trustees of the College were the senior Shippen, Thomas Bond, Thomas Cadwallader, Phineas Bond and John Redman.

A very close relationship existed between the college and the Pennsylvania Hospital, and Thomas Bond, interested alike in both, would welcome the pupils and graduates of the medical

The University of Pennsylvania, 1806–1829, showing the addition to the left, which housed part of the medical school. The main building was originally built to be Washington's house.

school attending his clinics in the latter, and this interest was shared by his colleagues. In this way, the hospital became the first clinical school of the College.

Before another commencement occurred, a young physician, Benjamin Rush, who had also earned his degree at Edinburgh, was coming home to become the professor of chemistry in the new school. The average age of the four professors was under 30 years.

The disordered condition of society attendant upon the Revolution, disturbed the quiet flow of scientific pursuits. Several of the professors of the Medical School went into the army. Morgan and Shippen successively acted as medical director-general and Rush as medical director of the middle department, the latter being one of those who signed the Declaration of Independence.

In these troublesome times of new freedom, the Charter of the College of Philadelphia was revoked by an act of the Legislature in November, 1779. This was the result of a feeling that the institution, being of colonial origin and patronage, needed thorough reorganization in order to place it on a basis harmonizing with the régime of Independence. The property of the College was transferred to a new institution.

The institution which took the place of the College of Philadelphia was called the "University of the State of Pennsylvania." The trustees of the new school at once directed attention to the medical department. They requested "the several Medical Professors in the mean time to proceed in their lectures as before." Dr. Shippen was the only one of the professors who at once accepted the position he had held in the Faculty of the College. Great difficulty was encountered in forming a faculty, and in October, 1781, Thomas Bond was "requested to unite Lectures on the Theory and Practice of Physic with his course of Clinical Lectures . . . until such time as a professor of that branch of medicine be appointed and undertake the business." This state of irregularity existed until November, 1783, when the former status of the professors was accepted by them.

Friends of the former College were successful in having the charter and property of the college restored in 1789, the new institution, however, retaining its position as a University, with its endowment from confiscated estates.

There existed then two medical schools with a somewhat interlocking faculty. Shippen taught in both schools; Kuhn only in the University, while Wistar took the chair of Chemistry at the College. James Hutchinson became professor of chemistry in the University, and Rush became professor of theory and practice in the College. Morgan died at this time. The College decided to abolish the degree of Bachelor of Medicine and to confer only the Doctorate.

The field for two establishments proved to be too restricted, and after party spirit had subsided and factional strife lulled to rest, it was realized that in union there would be additional strength. An amicable adjustment was brought about in September, 1791. It was agreed that the name of the united school was to be "The University of Pennsylvania." In the inaugural lecture delivered by Benjamin Rush in November, 1791, he said "I should do violence to my feeling should I proceed to the subjects of the ensuing course of lectures, without first congratulating you upon the union of the two Medical Schools of Philadelphia, under a Charter founded upon the most liberal concessions by the gentlemen who projected it. . . . By means of this event, the ancient harmony of the different professors of medicine

The University of Pennsylvania, 1829 to 1873. On the left is Medical Hall.

will be restored and their united efforts will be devoted, with accumulated force, towards the advancement of our Science."

The new faculty consisted of the professors of both schools. The announcement gave the professors and their subjects as follows:

Anatomy, Surgery and Midwifery	William Shippen, M.D. Casper Wistar, M.D., Adjunct.
Theory and Practice of Medicine	Adam Kuhn, M.D.
Institutes of Medicine and Clinical Medicine	Benjamin Rush, M.D.
Chemistry	James Hutchinson, M.D.
Materia Medica and Pharmacy	Samuel P. Griffiths, M.D.
Botany and Natural History	Benj. Smith Barton, M.D.

In 1805 a change was deemed to be expedient in the chair which had been held so long and honorably by Shippen. Surgery had remained in association with anatomy and obstetrics. Philip Syng Physick, who since 1794 had been one of the surgeons to the Pennsylvania Hospital, was elected professor of surgery. At this time the mother school in Edinburgh still combined anatomy and surgery in one chair. He filled the chair for 14 years, at which time he became professor of anatomy. One of his last major operations was one on Chief Justice Marshall for the removal of a stone in the bladder. Physick truly deserves the appellation so frequently applied to him "Father of American Surgery."

Shippen died in 1808. He had been a great teacher and had played a very important rôle in the early history of Philadelphia medicine. He was succeeded by Casper Wistar, who at first taught both anatomy and midwifery, but in 1810 the combined chair of anatomy and obstetrics was divided. Thomas Chalkley James was elected professor of midwifery, but it was not until 1813 that attendance upon his lectures was made obligatory for graduation. Wistar died in 1818. He was an ardent advocate of the use of models in teaching. His extensive group of models and specimens were presented to the University and were for years styled the Wistar Museum. It was greatly enlarged by two of Wistar's illustrious successors, Horner and Leidy. In 1819 the chair of surgery was awarded to William Gibson, who at the time was professor of surgery in the University of Maryland, whose School of Medicine was founded by Pennsylvania's first medical graduate, John Archer. Dewees, who had been adjunct professor of obstetrics, succeeded James in 1834. He was the first authoritative writer on this subject in America and may truly be regarded as the "Father of American Obstetrics."

With the separation of the important chairs into individual units, the School of Medicine of the University had begun the second period of its development. Those who succeeded maintained the high standard already set for them. The names of Horner, Leidy and Piersol, of Hare and Coxe; of Agnew, and John Ashhurst; of George B. Wood, Horatio C. Wood, of the William Peppers; Stille and Osler; of Mills and the Norrises; of Hodge, Goodell and R. A. F. Penrose; of Guiteras, Durhing, and many others fill an important niche in the history of American Medicine in the nineteenth century.

Philadelphia maintained its reputation as the medical center of the country. The splendid clinical instruction which had been begun in the Pennsylvania Hospital in 1766 by Thomas Bond, in connection with the medical lectures at the College, was expanded. The instruction was given at the bedside and in the clinical amphitheater.

Clinical opportunities were also afforded at the Philadelphia Almshouse (Blockley), now the Philadelphia General Hospital. It had gone into operation before the Pennsylvania Hospital, but not strictly as a hospital. In it was established the first obstetrical clinic for students, as early as 1770. For periods of time students were excluded but after 1805 every successive year found the prejudices, which had operated so long, more and more removed. The Managers with each succeeding year were seized with an active desire to foster and promote any method which contributed to the hospital's usefulness as a teaching institution.

In 1872 William Pepper, Jr., had the foresight to realize the importance of having a hospital

which should be an integral part of the Medical School. Largely through his efforts the present hospital of the University of Pennsylvania was built, the first hospital controlled by, and built for, a school in America.

Shippen's lectures had been delivered for years in apartments built in the rear of his father's home on Fourth Street. The other lectures were first probably given in the old Academy Building. The first building especially built for the use of the Medical Professors was situated on Fifth Street, and was called "Surgeon's Hall."

In 1802 the Medical School was partly moved to a former state building, built for the president, on Ninth Street, between Chestnut and Market Streets, and in 1806 an additional building was built on Ninth Street, and it was further enlarged in 1817. The school grew and accommodations rapidly became inadequate. The Trustees ordered that all buildings be removed and in 1829 built, what for many years, was known as Medical Hall. It was not until 1873 that the Medical School was moved to the present University site west of the Schuylkill River.

CORRESPONDENCE

FURTHER OBSERVATIONS ON THE RÔLE OF BILE IN HIGH INTESTINAL OBSTRUCTION

To the Editor: In a previous paper Benedict, Stewart and Cutner[1] reported the results of certain experiments on the rôle of bile in high intestinal obstruction. Although the results were not entirely conclusive they seemed to indicate that, when obstruction of the intestine was so high that no bile could be reabsorbed, benefit might be derived from administration of bile below the obstruction.

In the course of further experiments on high intestinal obstruction in dogs, all bile was diverted from the intestinal tract by cholecystostomy and ligation of the common bile duct. Obstruction of the intestine was carried out a week later by completely severing the bowel just below the ampulla of Vater, by inverting the proximal end, and sewing a catheter into the distal end for use as an enterostomy. Through this catheter, sufficient normal saline was administered twice a day to maintain water balance and normal blood chlorides. The cholecystostomy catheter was connected to a small rubber balloon and the bile withdrawn once a day.

One such animal survived for 38 days, at which time malnutrition probably was the most important factor in causing death. At no time was there any evidence of bile in the vomitus or stools, and autopsy revealed no accessory bile ducts. As this period of survival is longer than any heretofore reported in so high an intestinal obstruction the experiment would seem to disprove the theory that the presence of bile either above or below an obstruction of the intestine is a factor of any significance in the length of survival of the animal. Death in high intestinal obstruction, when the water and chloride balance is maintained, is probably due largely to malnutrition.

EDWARD B. BENEDICT, M.D.

Boston.

The author wishes to acknowledge with thanks the technical assistance of I. J. Thorne and D. G. Friend, students at the Harvard Medical School.

[1] Benedict, E. B., Stewart, C. P., and Cutner, P. N. The rôle of bile in high intestinal obstruction. Surg., Gynec. & Obst., 1932, liv, 605.

NEW MUSCLE-SPLITTING INCISION FOR RESECTION OF THE UPPER THORACIC SYMPATHETIC GANGLIA—A CORRECTION

In publishing this article in the March, 1933, issue, pages 651–657, a regrettable error was made which disarranged the order of the illustrations, certain of the plates appearing with incorrect legends. To correct the error the following changes should be noted: The plate appearing as Fig. 3 should be Fig. 1; Fig. 7 should be Fig. 2; Fig. 4 should be Fig. 3; Fig. 1 should be Fig. 4; Fig. 2 should be Fig. 7—EDITOR.

JOHN B. MURPHY

Material is being collected for an authorized biography of Dr. John B. Murphy. If any reader of this JOURNAL has in his possession letters from Dr. Murphy, knowledge of facts concerning his life, or any other data, it would be appreciated if they were sent to the Editors. All material will be returned promptly and the source credited.

SURGERY, GYNECOLOGY AND OBSTETRICS

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A DIFFERENTIAL DIAGNOSIS BETWEEN CERTAIN TYPES OF INFECTIOUS GANGRENE OF THE SKIN

WITH PARTICULAR REFERENCE TO HÆMOLYTIC STREPTOCOCCUS GANGRENE AND BACTERIAL SYNERGISTIC GANGRENE[1]

FRANK L. MELENEY, M.D., F.A.C.S., NEW YORK
Assistant Professor of Surgery, Columbia University

IN recent years there has been considerable interest in the problem of gangrene of the skin due to the invasion of micro-organisms. The literature in this field indicates that there has been great difficulty in the minds of some observers regarding the proper classification of these disorders. Many authors have reported late diagnosis, late institution of treatment, extensive destruction of tissue, long hospitalization, and high mortality. This is due partly to the fact that these diseases (except gas gangrene) are relatively rare, so that few observers have been able to report more than a single case. Confusion has further resulted from the fact that bacteriological studies have frequently been made so late in the course of the disease that it has been difficult to appraise the importance of the bacteria which have been found and frequently cultural methods have been used which were not suitable to reveal the significant organisms. It is with the purpose of clarifying this subject, to some extent, that the present paper is written, because the treatment of the various groups differs markedly and a delay in diagnosis results in a delay in instituting the proper treatment.

In infectious gangrene, bacteriological studies are essential if we are to learn anything about the pathogenesis of these infections and improve our method of treatment. These studies should be made early in the course of the disease and cultures should be taken from various parts of the lesion, particularly in the zone of advance. Anaerobic, as well as aerobic methods must be employed and culture media be used which is suitable for the growth of any organisms which may be present. It is obvious that this cannot be done in the great majority of cases, for many of them are seen either at home or in the office or in hospitals which are not fully equipped to make a complete bacteriological study. Furthermore the time required for the complete bacteriological analysis of any given case makes the study of little value as a basis of treatment for that particular case, particularly if the onset is sudden and the course is rapid. For all of these reasons it is essential that there should be a clinical differentiation by which any one seeing a case for the first time may recognize it at once and promptly institute the proper treatment. An attempt has been made, therefore, in the following paragraphs to give a practical clinical differentiation between certain types of infectious gangrenous processes of the skin and subcutaneous tissues.

The most important division of these cases is into acute and chronic groups. In the former a diagnosis should be made within a few

[1] From the Bacteriological Research Laboratory of the Department of Surgery, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York, New York.

hours. In the latter it may be safely made within a few days.

ACUTE GANGRENE

Acute infectious gangrene may be divided into two subgroups of great importance. These differ in so many features that they ought not to be confused. The first is relatively common: namely gas gangrene. It was seen during the war by every army surgeon. This is so well known in this generation that it is hardly necessary to go into details with regard to it in this paper except to differentiate it from the other groups. Let us hope that the coming era of World Peace under the League of Nations and the Pact of Paris will make it a rare disease.

GAS GANGRENE

Gas gangrene has recently been excellently reviewed by Wan and by Davison and individual cases have been reported by Linton, Shearer, Sarlin, Maes, and Butler. Gas gangrene not infrequently develops in a deep, punctured, or lacerated wound, which extends down into muscle and carries with it such foreign bodies as clothing, missiles, powder, or street dirt. A large proportion of the cases of gas gangrene in civil practice follow compound fractures. Likewise occasional cases develop after operation following the amputation of gangrenous lower extremities in diabetics or arteriosclerotics. The possibility of its development in these cases should always be kept in mind because certain precautions may be taken to prevent its occurrence and its early recognition is essential for its successful treatment.

Symptomatology. The onset of the disease is usually associated with an abrupt rise in temperature and pulse rate. The pulse approaches 120 and the fever reaches 103 to 105 degrees. There is general malaise, marked prostration and restlessness as well as apprehension. There is usually an increase of pain in the wound. This may be masked if the wound has been painful from the first. An examination of the wound usually reveals swelling and œdema with redness and acute tenderness. Gentle pressure on the margins of the wound usually produces a sanguinopurulent exudate in which gas bubbles may be seen. A smear made from this exudate will almost invariably reveal large numbers of large gram positive bacilli. Gentle palpation of the tissues may reveal crepitus, but this may not be appreciated in the early stages. An X-ray film will frequently demonstrate gas in the tissues even before it can be felt. To an experienced observer with a keenly discriminating sense of smell, there is a characteristic acrid or "mousy" odor.

When the infection has gained a foothold it spreads rapidly, the patient becomes very ill, fever remains high, the pulse rate increases, and crepitation around the wound is evident. This may advance appreciably from hour to hour. The spread of the disease is chiefly in the muscles. It may be confined to a single muscle from the wound margin up to its origin, leaving the neighboring muscles free but usually it spreads up the neighboring groups as well to a varying extent from the wound. The skin at the wound margin becomes first red and then dusky. The redness and œdema spread for a moderate distance around the wound but not extensively. Gradually the skin at the margin becomes dark and necrobiotic while the reddened area away from the margin takes on a yellowish brown or bronzed tint. Gangrene of the skin is generally limited to the margin of the wound and if the disease spreads extensively in the muscle, the gangrene of the skin slowly advances but it does not appear in isolated patches away from the margin. In untreated cases gas gangrene is rapidly progressive and almost invariably ends fatally.

Etiology. The gas gangrene organisms are anaerobic bacteria which differ from one another in their cultural characteristics and in the specific toxins which they form. There are four different species which are pathogenic for man and although they rarely occur in pure culture in gangrenous processes, they are believed to be able, alone, to produce the general and local symptoms of gas gangrene and their specific toxins may cause death. However, they are frequently associated with other organisms and there may be a synergistic action enhancing the virulence of the pathogenic anaerobes or the associated organisms. The most common of the gas gangrene organ-

isms is Bacillus aerogenes capsulatus (Clostridium welchii). The others are Bacillus œdematiens (Clostridium novyi), Vibrion septique (Clostridium œdematis maligni), and Bacillus sordellii (Clostridium œdematoides). The 3 last are more rarely found and if any one of these organisms is present, the local signs vary somewhat from that already described in that there is more œdema and induration of the tissues and less gas formation.

Treatment. With the earliest signs of this disease a stained smear of the exudate should be made if possible. If the signs are unmistakable or if in doubtful cases large gram positive bacilli are numerous in the smear, immediate operative interference is of the utmost importance. This procedure should not wait upon the cultural determination of the organisms. The wound should be completely excised and all foreign bodies and all necrotic tissue should be removed. Individual muscles should be explored and any inactive or devitalized muscle tissue should be removed. Anti-gas-gangrene serum should be used in large quantities. The serum which is now available is more potent and more concentrated than that which was formerly prepared and is effective against all of the known pathogenic gas gangrene organisms as well as tetanus. Concentrated monovalent and polyvalent sera are now available in "therapeutic doses." Depending on the severity and extent of the infection one or more "therapeutic doses" should be given intravenously as soon as the diagnosis is made and repeated every 8 hours until there is definite subsidence of local and general symptoms. If it is not possible to determine by culture what organisms are present, a polyvalent serum should be used, but if an analysis of the flora of the wound has been made, the specific antiserum should be administered in subsequent treatments.

There is a considerable difference in opinion as to whether amputation should be done in these cases. In certain regions of the body amputation is out of the question. However, even in a good many cases in which amputation may be done quickly and safely, if the disease is diagnosed soon after its development, amputation is not indicated. Adequate opening of the wound and removal of dead tissue and the administration of serum is frequently effective and results in the subsidence of the process. Although it is likely that amputation has been done in the severer cases, the statistics would seem to indicate that the mortality in amputated cases is not appreciably lower than in those in which that procedure is not employed.

HÆMOLYTIC STREPTOCOCCUS GANGRENE

Since the author's first report (60) in 1924, this infection has been described by Gage and by Jen, as well as in briefer reports by Mainzer, Bate, Fallon and Bettmann, and by the writer (61, 62). This disease may occur following a deep wound but is more likely to follow a much more trivial injury. Sometimes the injury is so slight that it appears to be a spontaneous infection but in general there is a history of a superficial injury of the skin, a scratch, a cut, or a hypodermic injection. It generally occurs on the extremities but may involve any part of the body. In the earlier literature some of these cases have been described as phlegmonous or gangrenous erysipelas but there are striking differences between this disease and erysipelas which will be brought out later.

Symptomatology. The disease is characterized by the sudden onset of pain and swelling at the site of injury. The part becomes red, hot, swollen, and heavy and while at first it may be very painful it later becomes numb or anæsthetic. The redness spreads rapidly during the first 2 days and may be very marked, but the margins fade out into the normal skin and are not raised as in erysipelas. The temperature generally does not rise over 101 to 102 degrees, except in rare instances when the illness is ushered in with a chill. Then the temperature may reach 103 to 104 degrees. On the other hand the pulse rate is rapid, frequently approaching 120. Prostration is marked but instead of irritability, there is usually a marked lassitude on the part of the patient. He becomes indifferent to his surroundings and has a total lack of appreciation of the severity of his illness. On the second, third, or fourth day the pathogno-

monic sign of the disease appears. *This should be watched for in any acute fulminating inflammation.* The sign is a dusky coloring of the skin appearing as a small purplish patch with irregular and ill defined margins. It may be some distance from the portal of entry. It has a bluish tinge which makes it distinct from the brilliant redness of the surrounding skin. At the same time a large blister or bulla may appear over this dusky area or somewhere else upon the red surface. These areas may extend very rapidly and changes in them may be seen from hour to hour. If proper treatment is not instituted at once other dusky patches may develop nearby, and these areas may later fuse so as to form a large plaque of gangrenous skin. In untreated cases about the seventh, eighth, or ninth day, if the patient survives, this necrotic skin becomes more sharply demarcated from the rest of the skin and a little later partial separation takes place along the edges. While the gangrene is developing, the diffuse redness continues to spread. The patient becomes more and more prostrated, fever ranges around 102 to 103 degrees, and metastatic foci may develop in the lungs, in joints, or elsewhere in the body. Frequent sites for these metastatic lesions are the subcutaneous tissues at pressure points or elsewhere. These metastases frequently form with very little redness but with a definite swelling and rapid formation of pus. In a few untreated cases the process comes to a standstill about the end of the second week, the slough separates, and large plaques of necrotic subcutaneous fat may separate beneath a relatively normal skin. But most untreated cases go on to rapidly overwhelming toxæmia with septicæmia, extensive metastases, and death. On the other hand, if proper treatment is instituted early, the whole process generally comes to an abrupt standstill and cases thought to be hopeless go on to rapid resolution and recovery. In the series of cases reported from China the mortality was 20 per cent but in the cases that I have seen in this country the mortality has approached 50 per cent. This higher mortality may indicate a difference in resistance to the hæmolytic streptococcus between Chinese and Americans or it may be simply a question of late recognition and late treatment. In the series which we reported from China the disease was so common that earlier recognition of it was possible. When an adequate operation was promptly performed, all of the cases which were not *in extremis* on admission responded satisfactorily to the treatment. With most of the cases which the writer has seen outside of the hospital, diagnosis has been made late and the treatment has been delayed or inadequate. Under these circumstances the prognosis must be guarded, for in such cases septicæmia is common and metastases frequent.

This disease is essentially a gangrene of the subcutaneous tissue with secondary gangrene of a part of the overlying skin, resulting from a thrombosis of the skin arteries which pass through the sloughing subcutaneous fat. The subcutaneous gangrene may extend for a long distance beyond the area of skin gangrene. Through this extensive subcutaneous slough patent blood vessels may be found supplying the relatively normal skin.

Etiology. The hæmolytic streptococcus is always found in these cases and in the great majority of cases it may be found in pure culture out in the advancing margin of the subcutaneous necrosis. Beyond the limit of subcutaneous necrosis there is a zone of redness and œdema which yields a sterile culture. This is in striking contrast to erysipelas for, in the latter disease, streptococci are most numerous in the advancing margin of redness and even beyond it in relatively normal skin. It must be assumed that in hæmolytic streptococcus gangrene there is a toxin widely diffusible in the skin and subcutaneous tissues which gives rise to the rapidly spreading zone of redness. In the early stages the hæmolytic streptococcus is also found in pure culture in the dusky areas of purplish discoloration and in the fluid of the blisters or bullæ. Later when the gangrene separates, other organisms may contaminate the field but usually do not spread widely. It is almost certain that these associated organisms play no part in the development of the disease and that it is, in fact, a pure hæmolytic streptococcus infection. The rapidity of its development and the extensive necrosis which it causes, suggest that

the peculiar characteristics of the onset of the infection may be due to a hypersensitivity similar to the Shwartzman phenomenon (82) or the Arthus phenomenon (3). Certain cases seem to illustrate one type and other cases the other. The allergic etiology has not yet been proved beyond question and it is difficult to prove because according to Shwartzman streptococci can produce the secondary necrotizing effect but cannot produce the primary sensitizing effect of the phenomenon. The sensitizing phase may be and probably is nonspecific. Another theory is that the organisms have some special predilection for the subcutaneous tissues or produce a ferment which acts quickly upon the subcutaneous connective tissue and fat. However, efforts which have been made to demonstrate such ferments have proved unsuccessful. These tests have not been done, however, with recently recovered strains of the organism.

Treatment. Surgery should not be delayed an hour after the diagnosis has been made. Contrary to the usual procedure either in erysipelas or in streptococcus cellulitis of the ordinary kind, longitudinal incision should be made at once through the gangrenous area and should extend in both directions just beyond the limits of the subcutaneous necrosis. Incision should be radical rather than conservative and long, single incisions serve the purpose better than multiple, small incisions in any given axis. The effect of these incisions is to relieve tension and at least partially to drain the involved area. This improves the blood supply and turns the flow of drainage away from the advancing margin. After operation, hot water soaks or hot poultices should be applied until the cellulitis subsides. This usually requires 2 to 3 days. Then Dakin's fluid should be applied by means of tubes or frequently changed compresses to favor the rapid separation of the slough. Each day as much of the slough as can be removed without bleeding, should be cut away. If incisions are early and adequate, the process will promptly subside and patients who look desperately ill when first seen, will show remarkable improvement and go on to complete recovery. But if operation is delayed for 24 hours after the pathognomonic signs appear, the chances of recovery will be greatly diminished and the extent of subsequent skin necrosis will be greatly increased.

Differential diagnosis. Fulminating types of gangrene generally fall either into the gas gangrene group or into the hæmolytic streptococcus gangrene group. They should not be confused, for in the former the injury is almost always deep and the invasion is largely in the muscular layers with gas formation and crepitation both in the muscle and in the subcutaneous tissues while the skin is relatively free. In hæmolytic streptococcus gangrene on the other hand the injury is usually superficial and the spread is almost always in the subcutaneous tissues with early involvement of the skin and without any crepitation. In gas gangrene the general symptoms are alarming and the local signs relatively mild. In hæmolytic streptococcus gangrene the local signs are alarming and the general symptoms relatively mild. While both infections are primarily due to specific organisms, infection may be rendered more severe by the association of other bacteria. However, in the case of gas gangrene these organisms generally gain a foothold at the same time or before the organisms of the gas gangrene group, whereas with hæmolytic streptococcus gangrene, the hæmolytic streptococcus is alone responsible for the initiation of the infection and secondary contaminants only grow after there has been a break at the margin of the gangrenous portion of the skin. Stained smears of the exudate in gas gangrene show many gram positive rods while in streptococcus gangrene the exudate contains only gram positive diplococci.

Hæmolytic streptococcus gangrene has been frequently confused with erysipelas, which is likewise caused by a hæmolytic streptococcus, but certain features sharply distinguish them. In both diseases, the onset is sudden but in erysipelas the general symptoms overshadow the local, there is usually a chill and a sudden rise of temperature to 103 to 105 degrees and the patient becomes apprehensive or irritable. In hæmolytic streptococcus gangrene the local symptoms overshadow the general, a chill is rare, the temperature does not often go as high as 103 degrees. The patient is indifferent rather than apprehensive

and dull rather than irritable. In erysipelas the redness starts in a small area and spreads perceptibly but rather slowly with a red raised margin at least in a part of its periphery. There is very little swelling of the part and the tissues are soft. As it spreads, the center becomes pale again. In hæmolytic streptococcus gangrene the onset is sudden, the affected part very rapidly becomes swollen and heavy, swelling and redness may spread up the whole extremity or widely over the body in 24 to 48 hours, but the margin of redness is not raised and is generally indistinct as it fades off into normal skin. The center does not become pale, but bullæ form and dusky areas appear on the third, fourth, or fifth day and go on to frank gangrene. Lymphangitis and lymphadenitis are rare but phlebitis is fairly common. In erysipelas, organisms may be cultivated at and beyond the spreading margin (95) but not in the center while in hæmolytic streptococcus gangrene there is a wide zone of redness in which cultures yield no growth but organisms are found in the blisters or bullæ and in the subcutaneous tissues out to the limit of the necrotic zone. Erysipelas may develop at any time during the course of this disease just as it may develop from any hæmolytic streptococcus wound. The writer has seen it just three times in the 45 or 50 cases of hæmolytic streptococcus gangrene which have come under his observation.

It seems likely that Fournier's cases of gangrene of the scrotum, penis, and vulva belonged to the hæmolytic streptococcus gangrene group. When he made his early reports, the cause was not known, but some of Fournier's pupils who studied the disease in later years, believed the streptococcus to be responsible. Bodin, however, reported a case of gangrene of the vulva in which there were not only streptococci but fusiform bacilli and spirilla which he thought were significant. Milian and Nativelle believe that they have found a specific organism of the Bacillus proteus group which produces gangrene of the skin in animals, and is, they think, the important factor in human gangrene of the skin. However, in 13 of 14, they found it associated with a streptococcus (not further classified) and they admit that they believe that "the streptococcus opened the door to the invasion of this organism." They found their organism in cases which were not at all alike clinically. Some were acute and others chronic. The acute cases which they describe may very well fall into the hæmolytic streptococcus gangrene group. The organism which they found seems more likely to have been a secondary invader. Culturally it can hardly be distinguished from other organisms of the Bacillus proteus group. It grows aerobically and profusely in all media. It spreads very quickly over a blood agar plate and, when present, makes the recovery of associated organisms very difficult. This prolific growth would lead one to believe that when it is *not* found it is surely absent from the lesion. This can not be said of organisms more difficult to grow or organisms requiring anaerobic environment. The fact that Milian's organism was not recovered more often in the series of streptococcus gangrene cases seen by the writer in China which were previously reported (60) and is not often found in gas gangrene, would seem to indicate that it is not a common or an important factor in the production of either of these forms of gangrene. Although it may occur more often in gangrene of the scrotum than in gangrene elsewhere because of the proximity of the anus, it was absent in the two cases of fulminating gangrene of the scrotum which the author has seen, both of which were typical hæmolytic streptococcus gangrene. Bodin also, in reviewing the subject of fulminating gangrene of the genitals, does not concede the theory of Milian and Nativelle that their Bacillus gangrenæ cutis (which was absent in his case) is of any significance as the cause of fulminating gangrene of the genitals.

The differential diagnosis of these acute diseases may be conveniently summarized in chart form (Table I).

CHRONIC GANGRENE

Cases of chronic infectious gangrene may be classified into three or four important subdivisions. Their differentiation is clinically more difficult than that of the acute cases. Each type has a number of distinguishing characteristics although in some instances the diagnosis may have to await a bacteriological

TABLE I.—DIFFERENTIATION OF ACUTE CASES

Name	Etiology	Symptomatology	Pathology	Treatment
Gas gangrene	Deep wound into muscle. Gram positive spore forming anaerobic rods. Early development of various kinds of associated bacteria.	Sudden onset. Profound general symptoms. High fever, rapid pulse, apprehension, irritability. Relatively mild local signs. Limited redness, swelling, and œdema of skin. Crepitation. Dusky wound margins. Bronzing of skin. Limited gangrene.	Extensive death of muscle. Fibers broken by gas formation. May spread whole length of a single muscle. Exudate loaded with gram positive rods. Relatively few pus cells. Negative chemotaxis for W.B.C.	Prompt operation. Removal of all foreign bodies and dead tissue. Complete débridement of wound. Early administration of large quantities of polyvalent or specific serum.
Hæmolytic streptococcus gangrene	Superficial wound. Pure culture hæmolytic streptococcus. No other bacteria or late occurrence of a few other species after gangrenous skin has separated.	Sudden onset. Relatively mild general symptoms. Low fever but rapid pulse. Lassitude, indifference, somnolence. Alarming local signs. Extreme redness and œdema without sharp margins. Irregular dusky areas on third, fourth, or fifth day. Blisters and bullæ. Rapidly developing extensive gangrene.	Extensive necrosis of subcutaneous tissues with a wide zone of sterile œdema beyond the limits of necrosis. Heavy exudation of fluid and polymorphonuclears at first and later large mononuclear phagocytes. Bacteria found all through the necrotic subcutaneous fat and in the blisters and bullæ. Thrombosis of some of blood vessels to overlying skin which becomes gangrenous.	Prompt operation. Long incisions to the limits of the subcutaneous necrosis. Release of all tension. Removal of necrotic tissue as soon as possible with a minimum of bleeding. Hot applications of moist heat until subsidence of cellulitis. Skin grafting if defect is extensive.
Erysipelas	Superficial wound. Pure culture of hæmolytic streptococcus. No associated bacteria.	Sudden onset. Profound general symptoms. Chill. High fever. Rapid pulse. Apprehension. Irritability. Slowly but steadily spreading area of redness with little or no swelling. Sharp raised margins.	Slight swelling and thickening of skin. No œdema of subcutaneous fat. Bacteria in and beyond advancing zone and not in center of lesion.	No operation. Soothing local applications. Ultraviolet light. Serum in severe cases.

analysis. Fortunately, the progress of these diseases is slow and time is given for a bacteriological study which may be used as the basis for treatment. While all of these groups are characterized by some distinctive clinical features, it seems certain that in each type the characteristic lesions are produced not by one organism as in the acute cases but by a special combination of two or more organisms. These diseases may, therefore, be called synergistic infections. They may be conveniently named as follows: (1) postoperative progressive bacterial synergistic gangrene of the abdominal or chest wall; (2) gangrenous impetigo (echthyma); (3) fusospirochætal infection of the skin; (4) amœbic infection of the skin.

POSTOPERATIVE PROGRESSIVE BACTERIAL SYNERGISTIC GANGRENE

One of the most striking examples of chronic gangrene of the skin is that which occasionally follows the drainage of a deep abscess either in the peritoneal cavity or in the chest. Considerable interest has been taken in this condition since 1924 when Cullen described a case which was thought at the time to be first on record. It has been reported so frequently since then that there seems to be no doubt that it occurred frequently before that time and was reported but the titles as they appear in the *Index Medicus* or *Surgeon General's Library Index* fail to reveal these reports definitely and they are obscured by the great mass of literature on the general subject of gangrene. Since Cullen's publication, cases have been reported by Brewer and Meleney, Alexander, Shipley, Gillespie, Hellström, Freeman, Mayeda, and more recently by Ballin and Morse (Case 4), Lynn, Meleney (63), Baker and Terry, Horsley (Case 1), Carol, and Kappis (Case 3). In this group also belong the cases of Christopher, Ballin and Morse (Case 2), Poate, and Patterson, all of which involved the chest wall following the drainage of an empyema. A few cases have been reported which developed spontaneously, e.g., Luckett, and Kappis (Case 1), or after clean operations in poorly nourished tissue, e.g., Kappis (Case 2), or after operations on frankly infected tissue, e.g., Probstein and Seelig. Inasmuch as anaerobic cultures were not made in these cases and the clinical course is not perfectly clear we cannot say with certainty whether or not they belong in this group but it would seem to be possible for the organisms causing this infection to be introduced into the tissues of the abdominal wall from without rather than from a deep abscess.

Symptomatology. In the majority of the cases which have been reported, the gangrene has followed the drainage of a peritoneal

abscess. It usually begins to appear about the end of the first or second week after operation, either as an infection of the whole wound or as a localized induration about retention sutures. At first the wound becomes red, swollen, and tender. Within the next few days the wound margins or the stitch holes develop a carbunculoid indurated appearance. The center of activity becomes purplish in color while the outer zone takes on a brilliant red tint. The whole region becomes exquisitely tender. *This symptom is an outstanding feature of the disease.* Within a few days the purplish areas become frankly gangrenous. The color of the dead skin changes to a dirty greyish brown and the surface is dull like suede leather. The purple zone spreads outward into the red and as it does so the skin becomes swollen and stands up above the normal skin level. The central side of the purple zone, toward the gangrene, is sharply defined but on the outer side it fades off into the red zone which slowly advances in all directions. The gangrenous skin is firmly adherent to the purple zone and there is very little undermining of normal skin. As the process advances, the gangrenous skin liquefies on its inner margin so that, as it encroaches on the purple zone and the circumference of the whole lesion enlarges, the width of the three zones remain fairly constant. As the inner margin of the gangrenous zone liquefies, it leaves exposed a base of granulation tissue which gradually enlarges. The destruction of the dermis is not always complete and here and there some deep islands of epithelium, from sweat glands or hair follicles, may start patches of regenerating skin epithelium. Usually there is very little general reaction manifested either by fever or anæmia and the patient remains in fairly good general condition although as the process goes on, he is gradually worn down with discouragement and pain. The reports of all but the most recent cases indicate that the true nature of the lesion was not recognized until there had been extensive destruction of the skin. In several cases practically the whole surface of the abdominal wall, and in one case the whole back became involved. In a number of cases the lesion spread downward from the abdomen to the thigh.

Etiology. In most of the cases reported in the literature only routine bacteriological studies were made. They yielded a variety of organisms none of which seemed to be of special significance. Special methods, however, were used in the study of the second case reported by Brewer and the writer (11) as well as in a subsequent case (63) and since they yielded identical results the findings seem to be significant. In the study of these cases an effort was made to determine all of the organisms present not only in the gangrenous tissue but in the spreading periphery of the lesion. This was possible in the first case when, after conservative measures had been employed unsuccessfully, a wide excision of the lesion was done and the specimen taken immediately to the laboratory. Multiple cultures were then made from the subcutaneous fat at the periphery of the lesion inward toward the gangrenous zone. A microaerophilic non-hæmolytic streptococcus was found in pure culture at the periphery of the lesion, not only in the red zone but just beyond it in the relatively normal tissues at the very margin of the specimen and far from the area of gangrene. In the gangrenous tissue itself, this organism was found to be associated with a hæmolytic Staphylococcus aureus, and a diphtheroid bacillus. The diphtheroid bacillus was entirely non-pathogenic for animals when injected alone or with either of the other organisms. When the streptococcus and staphylococcus were injected in pure culture into animals, no lesion was produced but when half doses of each organism were combined and injected, a gangrenous process developed which spread during the course of 3 or 4 days and simulated, to a considerable degree, the lesion in man. With this demonstration that these organisms could do something together which they could not do alone, the theory was advanced that the disease was the result of a synergistic action of the two organisms, the non-hæmolytic micro-aerophilic streptococcus being the essential organism in the zone of advance, in some way preparing the ground for the gangrenous action of the combined organisms. When the second case appeared, an opportunity was given in a single case to study two lesions, both of which yielded the

same result. Again the micro-aerophilic non-hæmolytic streptococcus was found in pure culture at the periphery and it was associated with hæmolytic Staphylococcus aureus in the gangrenous area. No diphtheroids were found. The synergistic experiments already described were repeated in animals over and over again. This seemed to offer definite confirmation of the theory of bacterial synergism as the cause of this disease. It is hoped that other investigators, using the same methods elsewhere, will endeavor to confirm the findings. It should be remembered that this micro-aerophilic streptococcus is not a strict anaerobe and will grow aerobically after a number of artificial transplants in media with a reduced oxygen tension and it is quite possible that in some cases it may be obtained aerobically from the exudate at the gangrenous margin of the lesion, even on primary culture. I believe that this has been done in those cases which were reported to have yielded a non-hæmolytic streptococcus. But when a study is made of the periphery of the freshly excised lesion in the red zone, it is likely that this organism will only be obtained by anaerobic methods. It corresponds to Streptococcus evolutus of Prèvot (76).

In the 2 cases just summarized the organism which Milian and Nativelle described was not found. This would seem to indicate definitely that it is not a causative factor in this disease. It may, however, contaminate the wound just as Bacillus coli, Bacillus welchii or any other intestinal organism may occur in a wound without necessarily taking part in the infection. (See reports of Cases 1 and 2 in which this occurred and Case 3 in which it did not occur.)

Owing to the fact that a number of authors (e.g., Cole and Heideman) have reported the presence of amœbæ in similar lesions, a careful study made in all 5 of these specimens by three different well trained parasitologists and in none of the 5 cases personally seen by the writer has there been anything suggestive of the presence of amœbæ in the tissues or in the exudate. The writer believes that this lesion may be secondarily contaminated with the bacillus which Milian has described and also with amœbæ, but the evidence is strong that these are not essential for the production of the lesion. Practically all of these cases have occurred following the drainage of a deep abscess either in the peritoneum or in the chest. In the abdominal cases the organism presumably came from the intestine as it is a common inhabitant of the alimentary canal. In the chest cases the original source of the streptococcus would seem to be either from the mouth or from infected emboli which were thrown off from thrombosed vessels in the peritoneum.

Treatment. In most of the cases which have been reported the wounds were partially closed by suture. This tissue tension in the presence of contamination may have favored the establishment of the infection. This suggests as a prophylactic measure that all skin wounds be left unsutured when peritoneal abscesses or chronic empyemas or lung abscesses are drained. The chronicity of this condition has afforded the opportunity of trying to cure it by many methods. Certain of the reports reflect the ingenuity and persistence of the surgeons in using all sorts of chemical and serological agents both generally and locally in the face of a baffling problem. In almost every case conservative methods, including local excision of the gangrenous margins have failed to check the advance of this process but radical removal of the lesion, including the outer zone of redness, either with the knife or with the cautery has almost invariably resulted in prompt disappearance of the disease. The defect left by this radical operation has then very quickly responded to skin grafting. In the present state of our knowledge with regard to these infections, this treatment should be instituted within a few days after the diagnosis has been made. When we learn something more about the interaction of these organisms and find some way to interfere with their action, perhaps more conservative measures will be effective. The writer prefers the knife to the cautery because there is less injury to the tissues and healing does not have to wait upon the separation of the tissue which has been destroyed by the cautery. There is very little to choose between the scalpel and the "radio knife."

Fig. 1. Case 1. Note the two separate areas of gangrene firmly adherent at the scalloped margin. Immediately beyond that is the raised purple zone merging into a red zone which fades off into normal skin.

Recent cases. During the past year the writer has seen three more typical cases of this kind which will be briefly reported here:

Case 1. C. H. Presbyterian Hospital, Unit History No. 323125, a man 63 years of age, a private patient of Dr. F. B. St. John, came to the hospital in December, 1931, with a 6 month history of increasing difficulty in bowel movement. It was found that he had a carcinoma of the sigmoid colon with considerable dilatation of the gut above it. A preliminary cæcostomy was done with a tube held in the cæcal wall by two pursestring sutures. Two sutures were taken in the external oblique aponeurosis and two in the skin. On the eighth day, the upper angle of the cæcostomy incision was found to be red and swollen; the skin sutures were removed. On the twelfth day the upper margin of the wound at the outer end became purplish in color around the outer suture hole while the inner end of the wound began to show evidences of early involvement. The whole area became red, swollen, and exquisitely tender. Within a few days the margin of the wound and the area around the stitch hole became frankly gangrenous and the purplish zone and red zone gradually spread outward. Just at that time an almost fatal coronary episode diverted attention from the wound. The process continued to spread slowly in two directions from the upper and lower ends of the wound. On the twenty-seventh day the writer was asked to see the patient, at which time the lesion had the following appearance (see Fig. 1.): There was a large involved area in the right lower quadrant which was oval in shape and oblique in direction corresponding to the incision made for the cæcostomy. At the inner and outer ends there were two areas of gangrene which were separated from one another; a circular one at the lower end, and an oval one at the upper. The lower and outer margin of the wound was slightly rolled in and the fæcal fistula, about 1 centimeter in diameter, near the center of the wound, was surrounded by pale granulations. In the two gangrenous areas the dead skin was firmly adherent. (In the lower lesion it measured about 2 to 3 centimeters in diameter and on the upper lesion about 2 by 6 centimeters. The outer margin of gangrene was scalloped at the line of demarcation and the living skin for a distance of 2 to 3 millimeters was dark purple. Beyond that for a distance varying from 5 to 10 millimeters there was a grayish purplish zone which stood up from the skin surface like a plateau. Beyond that the skin was very red for a distance varying from 2 centimeters below to 5 centimeters above. The outer margin of redness was not clearly defined but faded off rather quickly into normal skin.

On the next day the whole lesion was excised with complete cessation of pain. The gangrenous process did not recur and 5 days later it was possible to proceed with a Mikulicz operation for the sigmoid carcinoma in the left lower quadrant. The denuded area on the right side rapidly granulated over and was covered with small skin grafts 3 weeks after excision.

When the lesion was removed, it was taken to the laboratory and careful cultures were made of the subcutaneous tissue in the periphery of the lesion, after the skin surface was painted with 7 per cent iodine and the deep surface was seared. In three different places the micro-aerophilic non-hæmolytic streptococcus (Streptococcus evolutus of Prèvot) was found in pure culture by anaerobic methods. Cultures from the gangrenous margin yielded a multiplicity of fæcal organisms and the plates were overgrown with Bacillus proteus so that further identification was impossible. A careful microscopic search for amœbæ on the surface of the lesion and in the tissues revealed nothing resembling those organisms. Staphylococci and streptococci were abundant in the tissues at the gangrenous margin and streptococci were found in smaller numbers out toward the periphery of the lesion.

Case 2. A private patient of Dr. Russell L. Schmitt, Morristown, New York, a single, American school teacher of 62 years was admitted to the Horton Memorial Hospital, Morristown, New York, on August 11, 1931, as Patient No. 450 with a diagnosis of acute appendicitis with abscess. Operation was performed immediately after admission. A right rectus incision was used. The appendix was found extending downward over the brim of the pelvis and buried in a mass of adhesions including loops of the small intestine and possibly the and ovary. On separating these adhesions, the green

Fig. 2. Case 2. Note the lower right rectus incision and the large area of granulations surrounded by a large horseshoe shaped zone of gangrene extending almost to the costal margin. Beyond the gangrene there is a raised purple zone merging into a brilliant red zone which fades off into normal skin. On the surface of the granulation tissue there are three small areas of regenerating epithelium which are not clearly shown.

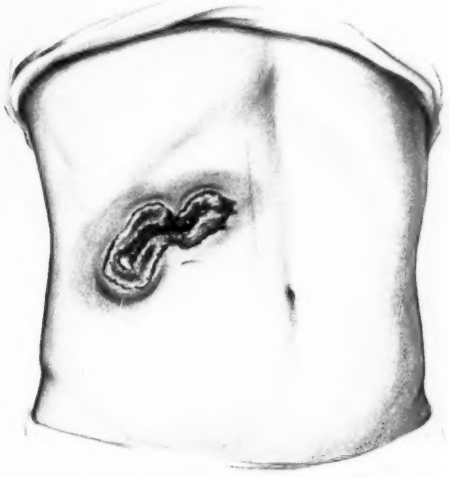

Fig. 3. Case 3. Note the upper right rectus incision which has healed and the lateral stab wound used for drainage. The area of gangrene is bilobed corresponding to the retention sutures of the second operation. The zone of gangrene is scalloped at the outer margin where it is firmly attached to the raised purple zone. Beyond that there is a wide zone of redness extending up over the ribs margin and across the scar of the first operation. The granulation tissue is narrow with the drainage opening at the upper end.

pus was liberated and a necrotic appendix was released and removed. Two cigarette drains were placed down to the abscess. Dermal sutures were used for the skin.

The wound drained copiously. On the fifth day after operation the patient complained of soreness in the wound. The discharge seemed to be fæcal. The skin edges became inflamed, so the skin sutures were removed and the wound edges were separated. The inflammation increased and the wound margins gradually developed a carbuncular appearance. Dressings became extremely painful, the edges of the wound then gradually became gangrenous and a line of demarcation appeared. Around the area of gangrene was a purple zone and outside of that the skin was very red for a distance of ½ to 1 inch. These zones gradually spread outward and the inner margin of the gangrenous skin liquefied leaving a floor of granulation tissue. During the next 65 days, in spite of all kinds of local applications and general measures to build up the patient's resistance, the lesion continued slowly to progress. By the seventieth postoperative day the gangrene had extended to include most of the skin of the abdominal wall. The writer was then asked to see the patient. At that time the lesion presented the typical appearance in the spreading margin but the red and purple zones were narrower than in Case 1. The gangrenous zone varied in width from 0.5 to 4 centimeters. There was a large area of granulation tissue with three islands of regenerating epithelium (Fig. 2). Radical excision was advised and this was accomplished with a scalpel. The line of excision was carried well outside of the red zone. Cultures, which were made in the operating room from the line of incision on semi-solid 1 per cent dextrose veal agar, showed a pure growth of non-hæmolytic streptococci. Cultures made from the necrotic edge of tissue showed streptococci, staphylococci, and gram negative bacilli on several different media (blood agar, plain agar, dextrose agar, and plain and dextrose broth). These organisms were not further identified. The specimen was taken to New York and 4 hours later cultures were made from various parts of the lesion. All of the cultures were overgrown with Bacillus proteus but by differential heating this organism was killed and the micro-aerophilic streptococcus was recovered. The histologic examination of the tissues revealed staphylococci and streptococci in the tissues but no amœbæ were found after careful search. Following excision dakinized dressings were used for 6 weeks at which time the wound was clean. Thiersch grafts were then applied and the patient made a complete recovery.

CASE 3. A private patient of Dr. John H. Carlisle, Passaic, New Jersey. M. S., aged 57 years was admitted to the Passaic General Hospital, Passaic, New Jersey as Case No. 75668 on October 30, 1932. For 12 years the patient had suffered from duodenal ulcer. On two occasions X-rays were taken, which showed a definite ulcer in the first part of the duodenum. On the evening of October 29, he had a supper of oyster stew and went to bed fairly early,

feeling quite well. About midnight the ulcer perforated. He was not seen until the following morning and operation was performed at 1 p.m., 13 hours after the perforation.

A perforation was found on the anterior surface of the first part of the duodenum. A simple suture was done and reinforced with a flap of fat so that the closure was thought to be quite satisfactory. The wound was closed but drainage was provided through a stab wound on the right. This was thought necessary because the gall bladder and structures in Morrison's pouch were covered with fibrinoplastic exudate. Cultures were not taken. After operation he persisted in running a low temperature. On the twenty-seventh day it was evident that he had a subphrenic abscess and an intermuscular incision was made under the right ribs. When the peritoneum was opened, pus was immediately encountered. Culture from this pus yielded no growth with aerobic technique. No anaerobic cultures were made. No liver abscess could be made out. Two cigarette drains were placed in the abscess and the wound was closed in layers around the drains with two retention sutures for the skin. Following the drainage of the abscess, the temperature fell somewhat, but continued around 100 to 101 degrees in the afternoons. There was a profuse drainage of pus. On the fifth day the wound was swollen and showed marked infection. The drains and the skin sutures were removed. The next day the old stab wound scar broke down, discharging pus. On the eighth day, there was considerable necrosis of the wound margins, most marked where the tension sutures had been placed. The patient complained of a great deal of burning in the wound and in the abdominal wall extending back along the course of the spinal nerves. The necrotic margins were cut away and various antiseptics were used but the infection continued to spread. On the fourteenth day, the infection began to spread more rapidly toward the flank. A diagnosis of symbiotic gangrene was then made and the writer was called to see the patient. The lesion at this time appeared as follows: The upper right rectus incision was well healed. In the right upper quadrant there was an area showing a striking similarity to the lesion in Case 1 (see Fig. 3). There was a zone of gangrenous skin from 1 to 2 centimeters in width, a raised purple zone outside of it from 7 to 10 millimeters in diameter, and outside of that a brilliant red zone from 1 to 3 centimeters in width which gradually faded off into normal skin. There was a narrow strip of granulation tissue on the floor of the wound and a sinus opening near the center. Below this lesion there was a small scar representing the original drainage tract. A wide excision was advised and operation was performed within an hour. The line of excision was carried about 3 centimeters beyond the reddened area. The skin and superficial fat were excised down to the fascia. The wound was dressed with fine meshed gauze wet with Dakin's solution. On the sixth day the defect was covered with pinch skin grafts and rapidly epithelialized.

Before operation cultures were made from the pus at the mouth of the drainage tract and from the gangrenous skin. At the time of operation, bits of subcutaneous fat in the line of excision were cultured. After operation, the specimen was taken to New York and within an hour of the time of its removal the skin was painted with metaphen and the deep surface was seared and further cultures were made of the subcutaneous fat at varying distances from the margin of the specimen toward the gangrenous zone, approaching it from the deep surface as well as through the skin. Half of these cultures were incubated at 37.5 degrees C., aerobically and the other half in an anaerobic jar. From the drainage tract and from the slough, the micro-aerophilic non-hæmolytic streptococcus greatly predominated but was associated with hæmolytic and non-hæmolytic Staphylococcus aureus and Staphylococcus albus. From the subcutaneous fat away from the zone of gangrene, the micro-aerophilic non-hæmolytic streptococcus was found in pure culture in 3 of 5 taken from the skin side and in 4 of 5 taken from the deep surface. In 2 of the 5 from the skin side, it was associated with aerobic spore forming rods, evidently skin contaminating organisms which resisted the iodine. In the fifth culture from the deep surface the streptococcus was associated with a Staphylococcus albus. The cultures from the line of excision in this case yielded no growth. A careful study of the tissue taken for pathological examination failed to reveal anything resembling amœbæ.

All 3 of these cases yielded the microphilic streptococcus in pure culture at the periphery of the lesion. Two of them were contaminated by a bacillus of the proteus group in the area of gangrene which made difficult the demonstration of other organisms although staphylococci were seen in the tissue sections and in the mixed culture. The third case did not yield a bacillus of the proteus group but yielded Staphylococcus aureus and albus in the slough. We believe that these 3 cases simply confirm the conclusions reached after study of the 2 cases previously reported, namely, that the essential organism in this lesion is the micro-aerophilic non-hæmolytic Streptococcus evolutus (Prèvot) but that the gangrene which is characteristic of the infection occurs only when this organism is in symbiosis with some other species—generally some variety of staphyloccus.

GANGRENOUS IMPETIGO (ECHTHYMA)

For a good many years reports have appeared in the literature describing a chronic gangrenous disease of the skin appearing in

undernourished individuals both young and old who were generally in a low state of nutrition and were frequently suffering from recurrent attacks of dysentery. It has been given many names by the dermatologists, among them, echthyma, pyoderma gangrenosum, impetigo gangrenosum, dermatitis gangrenosa, etc., etc. Recently such cases have been described in the periodical literature by Hartzell, Kitschmann and Kreibich, Wende and Bentz, Hu, Brunsting, Goeckerman and O'Leary, Morrissey and Reynolds, McCarthy and Fields and others. Most of the textbooks, Unna, Stelwagon, Sutton, MacLeod, Hazen, and Andrews have stated that this disease is simply a severer and deeper form of impetigo, but Shamberg was of the opinion that they were distinct.

Symptomatology. The lesions are usually multiple, and show various stages of development, one lesion following another in rather rapid succession. They occur most frequently on the scalp, face, and abdomen, but may be found on any part of the body. They generally start as small vesicles surrounded by a red zone. The center then becomes dark and gangrenous and depressed. The lesion increases in size slightly and occasionally two or three neighboring lesions may coalesce, but even the coalesced lesions seldom measure more than 1 or 2 centimeters in diameter. The disease is contagious and frequently occurs in several members of a family at the same time. Likewise the patient inoculates other areas of his body. As new lesions develop, the old ones frequently dry, the necrotic skin comes off as a scab, and a scar is left behind. The larger and deeper lesions, however, may persist for a long time. The gangrenous center then separates at the margin leaving a ring of depressed ulceration from the center of which the gangrenous plaque stands up like a button. If this separates from its base, a clean ulcer is left which slowly heals. This condition may last for months or years with exacerbations and remissions and frequently a crop of small fresh gangrenous lesions may develop after a recurrence of diarrhœa or colitis.

Etiology. The cause of these lesions has been variously explained by different authors. Most dermatologists consider this condition to be a serious form of impetigo. The onset of the lesion with vesiculation makes this seem plausible. The organism generally attributed to be the cause of impetigo is the hæmolytic streptococcus. Some authors have attributed echthyma to the action of Bacillus pyocyaneus, others to staphylococci, and still others to other streptococci. One of these cases died with a general sepsis in which three different organisms were successively found in the blood (42). This finding leads to some uncertainty with regard to their rôle in the etiology of the disease. Leloir in 1880 found both staphylococci and streptococci in 5 of these cases but he was unable to produce the disease in animals with these organisms in pure culture and thought that there might be some other etiological agent. Brunsting, Goeckerman and O'Leary regularly found a hæmolytic streptococcus and a staphylococcus in the lesions and, following the suggestion which the writer made with regard to progressive postoperative gangrene, they attributed the disease to a synergistic action of these organisms. With these two organisms in combination they were able to produce similar lesions in animals. These authors did not explain the association of this disease with colitis or dysentery. Fox believed that if cultures are made early, while the lesions are still vesicular, the hæmolytic streptococcus will be found invariably in pure culture but later when the gangrene develops, staphylococci are present also. He did not suggest the possibility of synergism between the two. In studying this disease, anaerobic cultures have rarely been made.

Treatment. Hartzell's case, although it resembled the others in its onset, differed from them in that excision of the lesions was the only method which effected their disappearance. He said that when the lesions were thoroughly excised, together with a considerable margin of sound skin, the wound thus made, rapidly healed. If, however, all of the infected tissues were not removed, as happened frequently, the wound became a steadily enlarging gangrenous ulcer with firm elevated borders like those which resulted from untreated lesions. There was no bacteriological study of Hartzell's case. Hartzell has been the only one to advocate complete excision of

these lesions, and his case may have been different from the others; for in almost all of the other cases reported, there was spontaneous healing following the separation of the necrotic tissue. Various and sundry local medications have been applied by different authors most of which had some measure of success. In a good many cases, while the individual lesion healed, recurrences dragged on for months or years. Most of the writers, however, believe that the majority of these cases will recover if general nutritional measures are instituted and if the usual methods of treating impetigo are continued industriously.

FUSOSPIROCHÆTAL INFECTION OF THE SKIN

A third type of chronic gangrene is represented by the foul infections developing in wounds made by human bites or in wounds which have been contaminated by mouth secretions. Leeuwenhoek was probably the first to observe the spirochætæ, the spirilla, and the fusiform bacilli which frequent the human mouth, but the classic work of Miller in 1890 offered the first comprehensive description of the mouth organisms. In 1894 Plaut (72) suggested the causative significance of the spirochæta and spirilla in certain of the non-diphtheritic infections of the throat and 4 years later, Vincent stressed the rôle of the fusiform bacilli without recognizing the prior observations of Plaut. In 1905 Plaut and Vincent debated the question. In 1896, Vincent (91) had observed spirochætæ in cases of hospital gangrene and believed them to be responsible for it. Eggers, in 1915, in the course of a morphological study of over 2,000 smears from chronic skin ulcers in patients in various parts of China, found spirochætæ in about 10 per cent. They were frequently found in the lesions commonly known as "tropical sore." Plaut (74) later found the combination of fusiform bacilli and spirochætæ in two "noma-like" lesions of the skin.

Stiles and Hassall, in their classification of the protozoa reported for man, state that the spirochætæ which are pathogenic for man are limited to the Treponema and Leptospira groups. Smith, in his recent book on fusospirochætal diseases, lists four species of spirochætæ and three types of fusiform bacilli, which occur in the human mouth and which have been found in human infections.

Hospital gangrene practically disappeared when surgeons began to have a little understanding of bacterial contagion and infection. It is almost certain, therefore, that it was an infectious type of gangrene. Whether or not it was due to a specific organism or to a specific combination of organisms not including the spirochætæ or to the fuso-spirochætal group as Vincent claimed may never be determined. Warren believed that the term included a number of different acute and subacute forms of infectious gangrene. The writer cannot add anything to the solution of this problem from personal experience but agrees with Warren after studying a number of the reports which appeared in the medical literature following the Civil War and later.

In recent years, gangrene of the skin and subcutaneous tissues, in which the fuso-spirochætal organisms play a part, has generally occurred following the implantation of mouth organisms into the tissues by human bites. Flick has recently reviewed the literature and added 5 cases to the ones which had been reported previously, by Hultgen; Peters; Hennesey, Madras, and Fletcher; Pilot and Meyer; Fuller and Cottrell; Bower and Lang.

A human bite invariably contaminates the wound with a mixture of organisms. Bates says that the police surgeons fear the severity of these infections more than any other type of infected wound. Usually gangrene does not develop in these cases unless there is a mixture of organisms which includes non-hæmolytic streptococci, fusiform bacilli, and spirochætæ. Although spirochætæ are never found alone in these infections the worst cases are certainly those in which spirochætæ are present. The infection almost always occurs either when a human being voluntarily bites another or strikes a blow with the hand which is cut by the teeth of the intended victim. The wound is usually a lacerated wound of considerable depth, but cases have been reported in which the injury was very superficial and one case followed the picking of a superficial blister with a pen knife with which the patient was accustomed to pick his teeth. It is surprising

that more wicked infections do not develop in wounds which have been sucked, for this is a common practice. It is probable that organisms are not planted in the depths by this procedure.

Symptomatology. There is usually some evidence of inflammation within the first 2 or 3 days after receipt of the injury and this steadily progresses. The exudate becomes foul, the margins of the wound are shaggy, bleed easily, and take on a dark grey-green appearance. The infection may spread fairly rapidly into the neighboring bones and joints. It burrows down into the deep spaces and may work up again toward the surface and break out at some distance from the original wound. Thus multiple sinuses are produced or if incisions are made in various places, the wounds remain open and continue to discharge the foul smelling exudate. Unless the proper treatment is instituted, these infections go on steadily for weeks or months with a progressive destruction, not only of the skin and subcutaneous tissue, but of the deeper structures.

Etiology. If smears are made from the foul exudate countless organisms are seen, among them streptococci, fusiform bacilli, and spirochætæ—the latter are better seen with the darkfield illumination. These organisms will develop only under anaerobic conditions and are grown best in or on special media. A great many serious human bites occur in which only streptococci and staphylococci are found but usually in these cases, although infection is severe and the general symptoms marked, there is no gangrene of the tissues. Although hæmolytic streptococcus gangrene might develop after a human bite, such a case has not come into the experience of the writer. If gangrene is present, either the fusiform bacilli or the spirochætæ are usually to be found and the severer cases harbor both of these organisms. There has been some debate among the investigators of these Plaut-Vincent infections as to whether the fusiform bacilli and spirochætæ are two different organisms growing in symbiosis or represent two different stages of the same organism. Tunnicliff is of the opinion that spirochætæ develop from the fusiform bacilli. She reports that she has actually seen this development taking place. However, this has not been confirmed by other writers who claim that although twisted forms of the fusiform bacilli do appear in old cultures, the spirochætæ which occur in these infections represent a different species and that it is a true symbiotic infection. Knorr goes further in stating that he has never seen a case of infection with either fusiform bacilli or the spirochætæ without streptococci being present also. He believes these infections are symbiotic in nature and that the streptococcus plays a necessary and an important rôle.

Treatment. Bates, who has had considerable experience with infections of this kind, now treats wounds caused by human teeth with radical excision as soon as they come to him. This, he believes, is an important prophylactic measure. When the infection has already gained a foot-hold, most authors have found that any temporizing measure is unsuccessful and they advocate fairly radical surgery which generally involves amputation of a finger or hand. The presence of spirochætæ has suggested the treatment of these infections with spirochæto-cidal chemical substances and although arsphenamine has frequently been used without success, better results have been obtained with neo-arsphenamine. This should certainly be tried before any radical surgical procedures are used, but temporizing measures should not be continued if there is no very definite improvement. Otherwise extensive destruction of important structures may take place.

AMŒBIC INFECTION OF THE SKIN

The ulcerative lesions of the intestine in which Endamœba histolytica is found are well known. The most frequent parenteral site for the activity of this protozoön is in the liver and the lesion within that organ may be a single abscess or multiple abscesses. It is of interest that all efforts made toward artificial cultivation of amœbæ in the absence of other organisms has failed. Likewise in the lesions within the body, the amœbæ are almost always associated with some of the intestinal bacterial species (in symbiosis). In the early stages, the liver abscesses frequently yield these associated organisms on culture and the presence

of the amœbæ is not suspected. In later stages after the infection has become established, cultures may fail to reveal bacterial organisms but scrapings of the abscess wall will yield living amœbæ. It seems to be possible, therefore, for the amœbæ alone to maintain a lesion in the human body, although in many of these cases there may be anaerobic organisms present which have not been revealed by culture.

Amœbic infection of the skin has been described by a number of authors practicing in regions in which amœbic disease is common. In most of the cases which have been reported, the involvement of the skin has been secondary to the spontaneous or operative drainage of a liver abscess. Such cases have been described by Heimberger, Nasse, Daborn and Heymann, Heymann and Ricou, Gauducheau, Carmini, Ch'eng, Engman, Jr. and Henry Meleney, and others. A few cases of skin infection have followed some operative procedure on the large gut, e.g., Cole and Heideman, Marwits and Van Steenis. By two observers, Maxwell and van Hoof, fistulas about the anus have been attributed to the action of amœbæ.

Gangrenous lesions of the skin attributed to amœbæ, which seemed to arise without any direct connection with an internal focus of the disease, have been listed only twice in the recent literature. In 1919, Engman, Sr. and Heithaus reported a case which came under their observation and they fully described the course of the infection. In this case, the disease developed secondarily in several of the lesions of impetigo from which the patient had been suffering. The amœba which they described was assumed to be but was not definitely classified as Endamœba histolytica. They included in their report 2 other cases, which may belong to this group but the evidence is not perfectly clear. Similarly in a case reported by Hansen and Stark the findings are not absolutely convincing because the organisms were not found in the lesions, although they were said to be present in the stools.

Symptomatology. In the cases which develop a gangrenous lesion of the skin secondary to the drainage of a deeper focus, there is always a period of days or weeks during which there is no specific change in the wound. The drainage tract becomes red, swollen, and painful in a manner similar to that in many drained wounds. Then the edges become indurated, everted and raised above the surrounding skin which takes on a dark brown color with hyperpigmentation. As the necrosis spreads, the center of the lesion remains as an ulcerated surface covered with dark granulations having "a color resembling that of raw beef which has been exposed to the air for some time" (Heimberger). The surface is covered with foul smelling exudate of thick brownish blood tinged pus with shreds of necrotic tissue in it. Usually the chief involvement is in the skin and subcutaneous tissue but the muscle may be involved, in which case the whole wound becomes necrotic for a considerable depth, as in Engman, Jr. and Meleney's second case. In amœbic lesions which have no connection with a deep focus, Engman and Heithaus say that the infection with amœbæ apparently must be preceded by an established infection with other organisms. This at once suggests the possibility of a symbiotic rather than a specific action. In such a case the infection remains relatively superficial. The spread seems to be in the cutis while the epidermis is involved secondarily and gives way. Glairy pus in small droplets may be expressed from the margin of the ulceration. This is said to be quite characteristic of the infection. If the proper treatment is not instituted, the lesion continues to spread fairly rapidly in all directions until large areas are involved and the patient finally succumbs either to the involvement of a vital organ or to an intercurrent infection.

Etiology. In none of the cases, reviewed by the writer, which have been attributed to amœbæ have careful anaerobic as well as aerobic bacteriological studies been made. The bacterial factor either alone or in symbiosis with the amœbæ may not have been given the attention which it deserves. It seems to the writer that one or all of the following conditions should obtain before it can be fairly stated that amœbæ are participating actively in any infection: (1) There should be histological evidence of the invasion of the tissues by the amœbæ, or (2) they should be

found either by smear or culture in the advancing margin of the lesion, or (3) the lesion should respond to emetin treatment recognized as adequate for amœbic disease. The writer believes that the mere presence of amœbæ on the surface of the lesion or in the exudate is no more evidence of their participation in the infection than the presence of Bacillus coli, Bacillus welchii, Bacillus proteus, or any of the other intestinal organisms is evidence of their activity in the tissues about a fæcal fistula. In most of the cases in which amœbæ have been observed, there has been no accurate determination of the type of amœba but in those cases having a direct connection with amœbic lesion of the liver or gut it is frequently assumed that the organism is Endamœba histolytica. In the case of Heimberger and in the second case reported by Engman, Jr. and Henry Meleney, there seems to be little doubt that Endamœba histolytica was present and played an important rôle in the infection. It is of particular interest to note that in Engman and Heithaus's case, bacterial cultures yielded no growth aerobically. After such a long exposure to contamination it is surprising that there were not secondary contaminants capable of growth even if the organisms responsible for the impetigo had disappeared. The spectacular response both generally and locally to the emetin treatment in this case as well as in Heimberger's case is strong evidence in favor of the importance of the amœbæ in these infections. In the second case of Engman, Jr. and Henry Meleney the invasion by the amœbæ of the whole thickness of the abdominal wall including the muscle, is a strong argument in favor of the activity of the amœba in that case, although there was little response to emetin. The fatal outcome may have been due either to the extent of the amœbic lesion in the liver or the virulence of the associated hæmolytic streptococcus and Staphylococcus aureus in a patient with diabetes. In the first case presented by these authors although the organism found was almost certainly Endamœba histolytica, the evidence is not so clear that the amœba played an important rôle. No cultural studies were made of this lesion so that the factor of bacterial synergism could not be weighed or measured. The amœbæ were found in the pus and on the surface of the wound but not in the depths of the tissue nor were they found in the apparently healing ulcer in the gut. It may have been a surface contamination. On the other hand, the temporarily favorable response to emetin may indicate that the amœba played a partial rôle in the production of the lesion. In the case reported by Cole and Heideman, there is still less evidence that the amœba, which was found in the pus but was not classified, was a factor in the infection. The organism was present in the exudate but not in the tissues. There was little if any response to emetin treatment even though the pathology seemed to be localized in the skin lesion. The disease was finally controlled only by a wide cautery excision such as is required in the bacterial synergistic gangrene. No anaerobic cultural studies were made in this case but the onset and the clinical course were typical of the bacterial synergistic gangrene and similar to the 5 cases of that type mentioned previously in lesions of which no amœbæ were found after careful search by three parasitologists.

Treatment. In all cases of amœbic abscess of the liver, the possibility of skin necrosis after drainage must be kept in mind and precautions taken to avoid it. An attempt should be made to protect the skin wound at the time of operation. A two stage procedure might increase wound resistance to the infection. If a one stage operation is performed, there should be complete relaxation of the wound with no attempt to close the skin and subcutaneous tissues by suture. If pathogenic amœbæ have been found, emetin hydrochloride should be given intravenously. If this medication fails and the disease is localized to the surface lesion, it should be widely excised. In all of these cases inasmuch as the bacterial symbionts always play a rôle of greater or lesser importance, a careful bacteriological study of the lesion should be made before operation and cultures taken from various portions of specimen after excision if that procedure be necessary.

DIFFERENTIAL DIAGNOSIS

The differentiation between the groups of chronic infectious gangrene is difficult, particu-

TABLE II.—DIFFERENTIATION OF CHRONIC CASES

Name	Etiology	Symptomatology	Pathology	Treatment
Postoperative progressive bacterial synergistic gangrene	Essential organism micro-aerophilic non-hæmolytic streptococcus (S. evolutus), in the spreading periphery of the lesion, associated with staphylococcus in the zone of gangrene.	Usually follows drainage of peritoneal abscess, lung abscess, or chronic empyema. Wound margins or retention suture holes after one or two weeks take on a carbunculoid appearance finally differentiating into three skin zones, outer bright red, middle dusky purple, and inner gangrenous with a central area of granulation tissue. Excruciating pain.	Destruction of epidermis and upper layers of dermis occasionally leaving some deep remnants of epithelium which may later grow. Under gangrene, heavy polymorphonuclear exudation. Under purple zone, hæmorrhage. Under red zone, hyperæmia. Many staphylococci and streptococci under gangrene. Scattered streptococci in the periphery.	Extensive excision of the whole lesion well beyond the red zone of advance, either with the electric cautery-knife or with the scalpel. Skin grafting.
Gangrenous impetigo (echthyma)	Essential organisms hæmolytic streptococcus and hæmolytic staphylococcus.	Usually occurs in debilitated persons especially those suffering from chronic dysentery. Lesions are usually multiple and may coalesce but are seldom large. Start as vesicles going on rapidly to pustulation and gangrene.	Usually superficial destruction of tissue with drying of the gangrenous skin, scab formation, and separation. Moderate polymorphonuclear exudation. Local invasion of staphylococci and streptococci.	Removal of crusts. Intensive local application of ammoniated mercury ointment. General nutritional treatment.
Fusospirochætal gangrene	Essential organisms fusiform bacilli, spirilla, and spirochætæ, usually associated with non-hæmolytic streptococci.	Usually occurs in a wound contaminated with mouth secretions, e.g., human bite. Early inflammation with a gradual development of necrosis of wound edges with penetration to bones and joints.	Extensive sloughing of superficial and deep tissue with multiple sinus formation. Organisms profuse in exudate and in the necrotic tissues.	Intensive intravenous administration of neo-arsphenamine. Radical amputation if medication fails.
Amœbic infection with gangrene	Essential organism Endamœba histolytica associated with numerous streptococci, staphylococci, and fæcal organisms.	Usually follows the drainage of an amœbic abscess of the liver. Margins raised and everted. Granulations have appearance of raw beef covered with shreds of necrotic material. Glairy pus expressed from margin.	Extensive destruction of dermis with undermining and secondary destruction of epidermis. Polymorphonuclear exudation. Amœbæ and bacteria numerous in the exudate and in the tissues.	Intensive administration of emetin hydrochloride intravenously. Radical excision of the lesion if disease is limited to the skin and medication fails.

larly between the bacterial synergistic and the amœbic groups, both of which usually follow an operative procedure. In the bacterial synergistic group there is no history of amœbic infection or evidence of deep amœbic lesion, no amœbæ are found either in the stools or in the exudate from the lesion or in the tissues, and there is no response to emetin treatment. In the amœbic cases there is frequently a history of previous amœbic dysentery or a frank deep amœbic lesion. Amœbæ are frequently found in the stools as well as in the exudate from the wound and in the tissues; and the lesions may respond promptly, often surprisingly, to emetin treatment. In bacterial synergistic gangrene, the lesion is extensive but superficial and develops slowly. It does not invade the muscle and the base of the ulcerated center is composed of active granulations which frequently reveal isolated islands of regenerating epithelium. In the amœbic infections the lesion is usually deeper, it develops more rapidly, and it may involve the muscle. The granulations have a raw beef appearance and islands of regenerating epithelium are rare. Pressure on the margins produces glairy pus in which the amœbæ may be found. All of the cases of postoperative progressive bacterial synergistic gangrene which have been examined at the time of excision have yielded a micro-aerophilic non-hæmolytic streptococcus in pure culture in the spreading periphery of the lesion while cultures in the zone of gangrene have revealed this organism in association with others. As far as the writer is aware the advancing margin of the amœbic lesions has never been examined bacteriologically but the exudate almost invariably yields, beside the amœbæ, a combination of organisms which may contribute toward the severity of the infection. Until complete bacteriological studies have been made in amœbic cases there cannot be any satisfactory pathological or bacteriological differentiation between these two groups.

Gangrenous impetigo and fuso-spirochætal gangrene of the skin are more easily differentiated. The former almost always occurs in individuals suffering from some debilitating disease especially a chronic dysentery. The lesions are multiple and follow one another with great persistence over a period of months

or years. Fusospirochætal gangrene almost always develops in a wound deeply contaminated with human mouth secretions such as a human bite. Gangrenous impetigo usually starts as a vesicle which becomes gangrenous in a few days but does not spread widely or deeply. In fusospirochætal infection, the lesion progresses steadily and penetrates deeply to muscle, tendon, joint, and bone with a massive destruction of tissue. Multiple sinuses are prone to develop and persist. From the lesions of gangrenous impetigo, the hæmolytic streptococcus and staphylococcus may both be cultured. From the Plaut-Vincent infections fusiform bacilli, spirilla, and spirochætæ may be found on smear or culture or with the dark-field illumination but there is usually some type of streptococcus, generally non-hæmolytic, also present.

The differentiation of the types of chronic infectious gangrene may be conveniently summarized in chart form (Table II).

SUMMARY AND CONCLUSIONS

In this paper we have attempted to differentiate clinically as well as bacteriologically, the various types of gangrene of the skin and subcutaneous tissue due to the invasion of microorganisms. They may be conveniently divided into acute and chronic forms.

The acute types are essentially diseases caused by single bacterial species although their severity may be augmented by associated organisms. They comprise (a) gas gangrene and (b) hæmolytic streptococcus gangrene. Their differentiation from one another and from erysipelas is summarized in Table I.

The chronic types are essentially diseases due to a mixture of organisms growing in symbiosis. These organisms in pure culture are either innocuous or produce lesions which are not gangrenous. They comprise (a) progressive bacterial synergistic gangrene, (b) gangrenous impetigo, (c) fusospirochætal gangrene, and (d) amœbic infection of the skin. Their differentiation is summarized in Table II.

The early differentiation of these infectious forms of gangrene is essential in order that the proper treatment may be instituted early. For in that way extensive loss of tissue may be prevented, the duration of illness may be shortened, and lives may be saved.

Three additional cases of progressive postoperative bacterial synergistic gangrene are herein reported.

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REGENERATIVE CAPACITY OF THE EXTRAHEPATIC BILIARY TRACTS

Clinical and Experimental Study

GEORGE HALPERIN, M.D., M.S., F.A.C.S., Chicago
From the Department of Surgery of Northwestern University

OPERATIVE procedures required for the repair or reconstruction of the extrahepatic bile tracts present a number of difficult problems and, generally speaking, constitute a difficult and ungrateful chapter in surgery. Cicatricial stenosis and partial or complete obliteration of the common bile duct as well as of the hepatic duct, may be caused by the following conditions:

1. Congenital anomaly such as diverticulum of the common bile duct;

2. Benign and malignant neoplasms involving the common bile duct, the head of the pancreas, papilla of Vater, the gall bladder or the cystic duct;

3. Inflammatory conditions: (a) decubitus ulcer in the common duct caused by a stone, (b) inflammatory induration of the lower end of the common duct, result of a large, callous ulcer of duodenum, (c) acute or chronic indurative pancreatitis;

4. Postoperative strictures.

The first three groups are relatively rare. The greatest number of cases calling for repair or reconstruction is furnished by the postoperative group. The most frequent cause of postoperative stricture of the choledochus or the common hepatic duct is a technical error committed in a course of a cholecystectomy and passed unnoticed at the time. Occasionally stenosis has taken place after a supraduodenal choledochotomy done for exploration and removal of stones, regardless of whether the incision was drained or closed primarily. The use of a T-tube, especially if too early removed, has been a not infrequent cause.

There is a group of cases in which stenosis developed in spite of faultless technique and in the absence of complications. Here belong cases of phlegmonous inflammation of the extrahepatic bile ducts in which the suppurative process ordinarily limited to the gall bladder, extended to and involved the common bile duct. The stenosed duct in such an instance is analogous to a shrunken gall bladder the result of a purulent cholecystitis. It is noteworthy that such cases have been found only after an operative procedure and never primarily.

Much more difficult is the explanation of cases, fortunately rare, in which stenosis occurred after a meticulously carried out operation and in the absence of inflammatory adhesions. A possible explanation may be found in a constitutional predisposition to connective tissue hyperplasia. The use of a drain may be responsible in some instances for an excessive connective tissue reaction. As is well known, injury to the common or the hepatic duct in the course of a cholecystectomy has occurred in the hands of master surgeons and need not be charged to a lack of skill or care in the performance of the operation. Correct anatomical orientation is not always possible. Variations in the normal arrangement of bile ducts and blood vessels, particularly in the presence of inflammatory conditions, make the recognition of the essential structures very difficult, at times impossible. Rugge in an anatomical study, made at the suggestion of Koerte, examined 43 human cadavers and found that the cystic duct joined the common hepatic in one of three ways: (1) In 35 per cent of the cases at a sharp angle. (2) In 20 per cent the cystic ran parallel with the common hepatic for a variable distance before joining the latter. The two may be so closely bound as to make their separation difficult. It is this type that Delbet characterized as "canal double hepato-kystique." (3) In 45 per cent of the cases the cystic duct ran a spiral course and joined the hepatic on its left side.

The subject of anomalies was further studied with essentially similar results by Kunze, Descomps, Rio-Branco, Eisendrath, Behrend, and others.

The operative injury is most frequently the result of inclusion of a part or of the entire thickness of the common bile duct or of the hepatic in the grasp of the forceps or ligature intended for the cystic alone. Next in frequency is the attempt to grasp blindly a severed, retracted, and spurting cystic artery. The injury, if recognized at the time of operation, should be repaired immediately. Its later repair in a jaundiced patient with a tendency to cholæmic bleeding, and in the presence of baffling adhesions and altered anatomical relations, becomes an infinitely more difficult, if not an altogether hopeless task.

CLINICAL EVIDENCE REGARDING THE REGENERATIVE CAPACITY OF THE EXTRAHEPATIC BILE DUCTS

It is a well established fact that partial defects of the choledochus, especially if they be longitudinal, heal spontaneously and only rarely display a tendency to scar contraction. The difficult problem is presented by cases in which so much of the duct is stenosed or destroyed that an end-to-end anastomosis is impossible. If the gall bladder is available, a short-circuiting operation of cholecystogastrostomy or cholecysto-enterostomy saves the situation. Most of the cases under consideration, however, have had a previous cholecystectomy. Doyen, as early as 1892, did the first choledochorrhaphy over a buried tube. Halsted attempted the same in 1900. Both operations resulted in failure. When the gap between the proximal stump and the duodenum or the stomach is not too great, and if the duodenum can be mobilized, the problem is relatively simple, the *direct anastomosis* between the hepatic or the common duct and the duodenum giving excellent results. The first hepaticoduodenostomy was performed by Hans Kehr in 1902 (33), and was described in his "Die Geuebte Technic der Gallenstein-operationen." W. J. Mayo (46, 47) reported a successful hepaticoduodenostomy in 1905. The case was again reported 10 years later by himself and 16 years later Balfour reported the patient as being in perfect health. In cases in which a direct end-to-end anastomosis of the severed duct is impossible because of the extent destroyed, or because of inflammatory conditions, or adhesions which make mobilization of the duodenum impossible, artificial reconstruction of the duct is the only alternative left. For these difficult cases three methods have been advanced:

1. Plastic operation utilizing pedunculated flaps carved from the gall bladder wall, stomach wall, duodenum or jejunum, as well as the use of a transplanted vein, fascia, etc.

2. A two step operation consisting first of forming an external biliary fistula from the gall bladder, cystic, common, or the hepatic duct. This fistula is cored out at a second operation and is implanted into duodenum or stomach.

3. Bridging the gap between the two ends of a severed duct, or between the proximal stump of the duct and duodenum or stomach by means of a rubber tube.

Hans Kehr (33, 34) was the first successfully to employ a seromuscular flap from the stomach in one case (in 1907), and from the gall bladder in another, to cover a defect in the common bile duct. Stubenrauch, in 1906, successfully employed a flap carved from the stomach in one patient. His attempts to perform the same operation in dogs were not successful. The recent experiments of Schrager and Ivy with the flap method proved that this procedure was feasible at least in dogs, provided that a tube fashioned out of gastric mucosal layer only was used. Ivy (personal communication) doubts, however, that such tubes can be made fairly long without endangering their blood supply and thereby compromising the end-results. Furthermore, all of their dogs developed a hepatitis. Attractive as all of these methods may appear in theory or in animal experimentation, their practical application in human beings is seldom possible.

Priority in the use of the method of fistula implantation undoubtedly belongs to Czerny as correctly pointed out by Horgan in a recent monograph. Successful results with the method have been reported by Stubenrauch in 1906, by Kausch in 1914, and more recently by Lahey and by Walters. Kausch reported a case which functioned normally 1½ years later. It was his conviction, however, that

most of these fistulas, because of a poor blood supply, were doomed to necrosis. Walters had excellent results in 3 of 5 cases. The oldest was well 3 years and 9 months after the operation.

Lahey had six satisfactory results out of a total of 10 cases. He advises that the fistula be not dissected from the under surface of the liver from which, he states, it receives a good deal of its nourishment, which in turn helps to prevent contraction. Of particular interest to me is the finding by Lahey of spontaneous internal biliary fistulas in 4 of the cases, "the duodenum or stomach attaching itself to the hepatic duct above a stricture and a small and inadequate spontaneous fistulous canal being established between the two." They were in all 4 cases not of sufficient size to prevent back pressure and jaundice. The phenomenon is both interesting and suggestive. There appears to be a tendency on the part of the stomach and duodenum to attach themselves to the liver by means of adhesions, in the absence of a normal route for the flow of bile into the bowel, thus facilitating formation of a spontaneous biliary fistula into one or the other.

The use of a buried rubber tube to bridge the gap: The possibilities of this method, and the principles involved constitute the main object of this study.

REVIEW OF THE LITERATURE

This type of operation was performed for the first time in 1905 by Jenckel of Munich.

The patient, a woman, was operated on by Heinrich Braun for empyema of the gall bladder caused by a large solitary stone. The gall bladder was removed, the ducts did not appear to contain stones and were not opened. Five weeks later the patient developed jaundice and acholic stools. Eight months later, at a second operation, Jenckel found that the common duct was shrunken in its entire extent. The distance between the common hepatic duct and the duodenum amounted to about 8 centimeters. Because of the distance and the presence of numerous adhesions, a hepaticoduodenostomy appeared impossible. Jenckel inserted a rubber catheter into the larger of the two hepatics, the right one, and secured it there by a catgut suture. The lower end of the tube was laid on the duodenum and fixed to it by the method of Witzel's gastrostomy technique, its end being turned into the lumen of duodenum through a stab wound. Bile from the left hepatic duct was conducted outward along drains placed about it. The tube was removed digitally 32 days later and was replaced by another. In the removal, the duodenal wall was partly torn. This, however, seemed to favor the case. The duodenal mucosa proliferated so rapidly as to fill the edges of the wound. After a stormy course the patient had recovered and was reported as being entirely well 4½ years later.

The remarkable feature of the case was that a rubber tube was substituted for the common bile duct and that apparently a new duct formed about it. Jenckel concluded that a new epithelial lining had grown in from the two ends, the hepatic and the duodenal.

The next case in the literature is that of Jan Verhoogen of Brussels, reported by his assistant Van de Graeuwe in 1908.

The patient, a woman, 49 years of age, was operated on by Verhoogen because of jaundice of 3 months' duration. Verhoogen found a neoplasm involving the gall bladder, cystic, hepatic, and the common bile ducts. These were resected together with the choledochus and a portion of the common hepatic. The resulting gap between the stump of the hepatic duct and the distal stump of the common duct amounted to 6 centimeters. Verhoogen introduced a rubber tube 1 centimeter thick into the lower stump and passed it upward toward the hepatic. Just before the tube reached the latter it was fenestrated, bent at almost a right angle and led outward. This arrangement made it possible for bile to flow partly into the bowel, partly to the outside. The wound was carefully tamponed. The tampon was removed 5 days later, the rubber tube itself 12 days later. The patient was reported to be in excellent health 1 year later.

Verhoogen likewise concluded that epithelial regeneration had taken place, in his case from the ends of the hepatic and the common bile ducts. He likened the regenerative capacity of the bile duct to that of the urethra, and thought that the enlargement of the duct above the constriction was a favorable factor in epithelial regeneration.

Doberauer, in 1908, resected a carcinomatous growth involving the supraduodenal portion of the common bile duct, leaving a gap of 4 centimeters between the stump. As the ends could not be brought together, he introduced a rubber tube into the stumps securing it there by means of a few catgut sutures. The duct functioned for 3 months at the end of which time the patient succumbed to metastases.

Doberauer mentions one other case in the literature, that operated on by Kehr in 1905 and mentioned in his "Die Geuebte Technic der Gallensteinoperationen." In Kehr's case the gap, amounting to 6 centimeters, was bridged by a rubber tube sutured into the hepatic duct and introduced through a stab into the duodenum. The patient was well 2 years after the operation. In still another case reported by Liebold, Kehr approximated the posterior surfaces of the two ends with three sutures and then turned in a flap carved from the gall bladder to cover the defect in the anterior wall of the common duct.

Voelcker did not consider it safe to leave the catheter in. In his first case he solved the problem by leading the catheter out of the duodenum through a second stab and leading it out on to the skin.

Brewer, in 1910, reported 1 case and Wilms, in 1912, 6 cases, in which they employed the Jenckel procedure. The 2 last named authors have simultaneously adopted the step of allowing the buried tube to pass out of its own accord. In German literature this procedure is frequently referred to as the Wilms-Brewer operation. Wilms could explain the success in his cases only on the basis of the ability of the epithelium lining the ducts to regenerate rapidly along the prosthesis. McArthur, a pioneer in this work, particularly stressed the point that by constant duodenal and jejunal tug the catheter would ultimately be drawn into the intestine and be discharged per rectum. He reported eight successful choledochorrhaphies over a buried tube.

Feist has collected 24 cases of primary healing with the buried tube method up to 1925. To this number I have been able to add 18 more cases from the literature considered as successes by their authors. A brief summary with the postoperative periods reported, follows. Jenckel had 7 cases reported from his clinic by Gerlach as being well 8½, 7, 6½ years later, and shorter periods. Wilms reports 6 cases well for periods of from 3 months to 12 months. Verhoogen (10), 1 case, 1 year; Alessandri, 1 case, 6½ years; Doberauer, 1 case, 3 months; Kehr (34), 1 case, 2 years; Propping, 1 case, 2½ years; Hagyard, 1 case, 6 months; Feist, 1 case, 12 months; Voelcker, 2 cases; Lobmeyer, 1 case; Huebsch, 1 case; Martin du Pau, 1 case; Simon, 4 cases; Kuemmel, 1 case; Desplas, 1 case; Gernez, 1 case, 4½ years; and Mann, 1 case, well 5 months.

Three years after the first operation by Jenckel and 1 year before its publication (Jenckel did not publish it until 1910), Arthur G. Sullivan (59, 60) reported the operation successfully carried out in 8 dogs. The fact that Sullivan was undoubtedly the first to perform this operation in animal experiments, just as Jenckel was the first to perform it successfully in the human, suggests the propriety of calling it the Jenckel-Sullivan operation rather than the Wilms-Brewer operation.

The study of the cited cases prompts the following questions: Does a new duct form? Does the epithelium actually grow in to line the new channel? Does an ascending infection take place? What is the effect of a buried tube on the tissues? How long does the tube remain *in situ?* What happens after the tube passes? What are the end-results? It is only fair to state that the literature contains a number of reports recounting frank failures and condemning the method. Enderlen, Propping, and Arnsperger were pessimistic about its value[1]. Magnus reported 3 consecutive failures with it, and Naegeli, 2. Brewer's patient developed obstruction symptoms 2 months after the second operation and died of cholæmic bleeding. To these cases should be added those of Cahen and of Hagler, the patients dying of liver abscesses 5 and 7 months after the operation. It is safe to assume that failures are less likely to be reported than successes, and that a number of cases originally reported as successes subsequently developed stenosis with its dire effects.

Does a new duct actually form? Jenckel, Verhoogen, Wilms, Pels-Leuden, and others answer this question in the affirmative. The explanation according to them is to be seen in the extraordinary regenerative capacity of the epithelium of the extrahepatic bile tracts. The epithelium grows along the prosthesis from the stumps and forms a new epithelial channel. Verhoogen and Wilms see an analogy in the remarkable regenerative capacity of the epithelium lining the urethra. The same

[1]See discussion in Zentralbl. f. Chir., 1923, 19.

opinion is expressed by Judd and Burden as late as 1924, in a paper in which they discuss the histological structure of the common bile duct. They state, "The lining epithelium of the common bile duct is possessed of extraordinary power of regeneration and quickly covers any break in its continuity; in fact it grows into and lines a new duct constructed from other tissue, as was shown experimentally by Horsley."

I shall attempt to answer the question of new duct formation, as well as the question of epithelial regeneration, on the basis of postmortem evidence as well as on the basis of experimental data. In passing, I wish to quote an opinion advanced by W. J. Mayo (47) in 1916. In discussing the various methods of reconstruction of the common bile duct, he had this to say concerning the Sullivan method: "This is by all means the simplest method of restoring the bile channel, but unfortunately the newly formed channel is not mucus lined, and we must expect that eventually contraction will take place after the tube slips into the intestine, which will ultimately occur."

Does an ascending infection occur? It is my impression that more or less infection occurs in every case. It need not in every instance lead to liver abscesses, as in the cases of Cahen and Hagler, but that a variable amount of cholangeitis and hepatitis takes place is most evident from the frequent mention in the postoperative histories of these patients, of chills, fever, and jaundice. Jenckel and Wilms believe that formation of an oblique channel in the duodenal wall *a la* Witzel, will do much to prevent an ascending infection.

The use of a buried tube apparently does not favor formation of stones, but that it may lead to pressure necrosis is evident from at least two cases. Thus Freund removed a prosthesis which lay buried for 2 years and which led to stenosis of the papilla of Vater and caused attacks of jaundice and fever. Graff (cited by Feist) removed a tube in a case in which, after 10 years of good health, it led to formation of liver abscesses.

How soon does the tube pass? That depends principally upon the method of fixation and the kind of suture material used. There is no way of telling how long the tube remains in the intestinal tract after it has passed into the bowel. In some instances the tube was vomited up.

What happens after the tube passes, as well as the end-results themselves, cannot be accurately judged from clinical cases, reports of which are limited to short periods of observation. The answer to these is closely linked with the question of whether new ducts are actually formed, and whether these ducts are lined by epithelium.

From the evidence thus far educed, it is apparent that the much vaunted regenerative capacity of epithelium of the extrahepatic bile ducts is so far a conjecture rather than an established fact. There remain to be proved at least 2 facts, one, that new ducts have actually formed, and, two, that these newly formed ducts were lined by epithelium.

POSTMORTEM FINDINGS

In the consideration of many a clinical phenomenon we naturally turn to postmortem findings for elucidation. A search of the literature on this point brings to light 3 cases in which, after a reconstruction operation of the Jenckel-Sullivan type, a postmortem examination was made. In one of these a histological study of the new duct was made.

CASE 1. This case was reported in 1913 by Cahen. Cahen performed a cholecystectomy in a woman for a fibrotic gall bladder containing numerous stones. The common duct was explored and a tube inserted. A biliary fistula resulted. The fistula closed at times giving rise to chills, fever, pain, and vomiting. At a second operation, 7 months later, Cahen found a complete stenosis of the common duct. The patient's condition on the table was desperate. Numerous adhesions and the extent of the gap between the hilus of the liver and duodenum made a direct anastomosis impossible. Cahen sutured a rubber tube into the common hepatic and introduced its distal end into the stomach *a la* Witzel. The tube was vomited up about 1 month after the operation. There was an improvement as to symptoms for a short time, later followed by diarrhœa, loss of weight, and asthenia. Death took place 4 months after the operation.

Autopsy revealed that death was due to liver abscesses. In the duodenum, 1½ centimeters away from the pylorus, there was found a round opening about 4 millimeters in diameter. When a sound was passed, it led into the common hepatic duct. The papilla of Vater could not be found. The fistula between the hepatic duct and the stomach was com-

pletely obliterated. Instead there developed a communication between the hepatic duct and the duodenum.

Cahen believes that the tube had wandered away from the stomach after the catgut sutures had absorbed. The free end of the tube, according to him, now impinged upon the duodenal wall and caused a decubitus ulcer. After the expulsion of the tube from the stomach the oblique canal in the latter became obliterated and the bile found its way into duodenum through the ulcerated portion. The newly formed adhesions pulled up the duodenum close to the liver hilus. When we recall Lahey's experience with formation of spontaneous internal biliary fistulas, we feel that Cahen's exploration is perhaps unnecessarily complicated. The essential feature is the presence of adhesions which brought the duodenum up to the mouth of the hepatic duct. The formation of communication between the two was perhaps nothing more than the formation of a spontaneous internal biliary fistula when the anastomosis between the duct and the stomach become obliterated. Adhesions have approximated the common hepatic duct and duodenum and the effect of bile completed the formation of an anastomosis between the two. In other words, nature had apparently performed a sort of hepaticoduodenostomy. Cahen does not believe that epithelization of the new channel takes place. He feels that nature plays an important part in the reconstruction by pulling up the duodenum to the hilus of the liver through newly formed adhesions, thereby materially shortening the gap. No histological study was made.

The second case reported was that of Desplas.

He resected the hepatic duct for a malignant tumor of pancreatic origin. He inserted a Pezzar rubber catheter into the left hepatic without suturing it there. The distal end was introduced into the stomach, thus leaving from 8 to 10 centimeters of the tube running exposed in the peritoneal cavity. The exposed tube was covered by omentum. The patient recovered from jaundice and gained in weight. Later cachexia and ascites developed because of the presence of a malignant growth but jaundice did not return. Exitus took place 152 days after the operation.

Postmortem examination revealed a large tumor of the head of the pancreas. The duodeno-pylorus was adherent to the left biliary pedicle. Stomach, liver, pancreas, and duodenum were removed *en masse*. When the stomach was opened, the tube was found to have passed as far down as the third portion of the duodenum. Between the duodeno-pylorus and the hilus of the liver there had formed a fibrous channel which was found to be intact and which permitted the passage of a sound. Apparently, there had formed about the Pezzar catheter a fibrous channel establishing an anastomosis between the liver and the stomach. The stomach and the duodenum were pulled up by adhesions and adhered to the liver hilus.

Histological examination of the new hepatogastric channel revealed that its proximal portion toward the hepatic pedicle possessed an epithelial lining of the type of hepatic mucosa. The distal portion of the duct was lined by a mucosa containing Brunner's glands and resembling that of duodenal mucosa. One-half of a centimeter of its middle portion contained no epithelial lining, it was made up of connective tissue fibers only. In the liver were found biliary abscesses.

In the discussion Gernez related necropsy findings in his own case (third case).

He operated on a man 69 years of age, because of chronic jaundice. The gall bladder, cystic and the common ducts were replaced by fibrous tissue up to the common hepatic. Gernez inserted one end of the tube into the common hepatic duct, the other into the stomach. The patient was in good health for 4½ years, at the end of which time he developed jaundice and died. Postmortem examination revealed obliteration of the midportion of the new channel. No histological examination was made.

The findings in the 3 cases suggest that the most important factor in the favorable outcome is played by nature itself. I have again reference to the formation of adhesions which result in pulling up of duodenum and stomach to the liver. This materially shortens the gap between the two, bringing about a sort of hepaticoduodenostomy or choledochoduodenostomy or gastrostomy.

In only 1 case, that of Desplas, was a histological examination made. When one considers that the new channel was relatively short, the fact that its midportion was still devoid of epithelium 152 days after the operation, does not suggest much regenerative power on the part of the latter. It would be difficult under the circumstances to say whether the epithelium in its upper and lower portions was newly formed or old. In the third case stenosis took place in the mid-

portion of the new channel, probably because it contained, as in the case of Desplas, connective tissue only.

EXPERIMENTAL DATA

Sullivan (59, 60) was undoubtedly the first, in 1908, to perform in dogs the operation of uniting the common hepatic duct with duodenum by means of a buried rubber tube. His technique was as follows: the common duct was cut across and a rubber tube was introduced into and up into the common hepatic duct, and secured there by a stitch on either side. The tube ran freely in the peritoneal cavity down to the upper border of the first portion of duodenum to which it was secured after the manner of Witzel's gastrostomy. Its end was introduced into the lumen of duodenum through a stab wound. The exposed tube was covered by an omental flap. He had operated in this manner upon 8 dogs without a single mortality. Although he had 8 available animals, Sullivan subjected only 1 to a histological examination. This specimen was removed from a dog 10 days after the operation. His pathologist reported that, "the mucosa had grown upward from the duodenum and downward from the duct into the new formed tube. In its middle portion its walls are made up of peritoneal tissue."

Enderlen and Usti, in 1911, produced defects in the gall bladders of rabbits and dogs and covered them with an omental graft. After 19 days the graft was found to be completely covered by new epithelium. About this time formation of glands was noted. The new epithelium was of a low cuboidal type but later became high cylindrical. The graft showed connective tissue proliferation which later underwent contracture.

Arnsperger and Kimura, of Wilms' clinic, performed, in 1912, the Sullivan operation in dogs. The tube usually passed about the thirty-fifth day. Their animals died of peritonitis caused, in their opinion, by premature passage of the tube, bile leakage, or perforation of the new duct at a point at which the omental flap was not well applied. All of the animals developed a stenosis at the point where the new channel entered the duodenum. Only 1 dog did not develop obstruction and jaundice, and this one died of pneumonia 30 days after the operation. They state that epithelization did take place in some of the dogs, but do not mention any histological study. Gross inspection is obviously no reliable criterion.

In 1913, C. B. Davis and Dean Lewis made in dogs tubes of fascia taken from the sheath of the rectus muscle, and placed them about a defect in the common duct. In their first series 3 dogs survived 2 months. In a dog which survived 65 days, stenosis took place at the duodenal end. The fascia remained alive in all cases. The histological report was to come later.

In 1918, Horsley attempted in dogs to substitute an everted external jugular vein for the common bile duct. The vein was stitched to the common hepatic, and the distal end was introduced into the duodenum by a sort of modified Witzel technique. He operated in this manner on 16 dogs. Most of the animals died of bile leakage at the suture line of the duct with the vein. Horsley considered the final results unsatisfactory and invoked a biological law to explain the contracture which took place in every case in which the dog survived the operation. The irritating effect of bile upon tissues not adapted to it caused inflammation with subsequent contracture. In spite of the discouraging results Horsley states, "That epithelium does grow at least over a portion of the reconstructed duct is shown in one section (23 days old). Columnar epithelium has grown a considerable distance over on the transplanted vein."

Somewhat more ambitious experiments accompanied by photomicrographs of histological sections were reported by Seulberger and Poellwein in 1926. These authors made three groups of experiments: In group 1, anterior defects in the choledochus covered by omentum, they did not observe the slightest trace of epithelial regeneration in specimens 3, 91, and 113 days old. The defects were not very large. In groups 2 and 3, choledochogastrostomies and choledochoduodenostomies *a la* Sullivan, the newly formed ducts invariably became stenosed. No epithelization was noted in the granulation tube even in specimens 100 days old.

Latteri (39, 40) believed that diverting the

flow of bile away from the common duct would favor healing of defects. He performed a series of experiments in dogs in which a metallic tube was introduced into the common duct through a small incision in the gall bladder. The tube could be removed at a later date by means of a string attached to it. By means of two tight ligatures a portion of the common duct was caused to undergo necrosis. This area was covered by an omental graft. The tube was removed from 3 weeks to 2 months later. The animals were sacrificed 3 to 4 months after the operation. In 6 of 7 dogs the regenerated duct exhibited a complete mucosal lining. In spite of it, all of the ducts exhibited marked narrowing with dilatation above.

In a second series Latteri utilized the trachea of a guinea pig, of a lark, and a pigeon quill to bridge a 1 centimeter defect in the common duct of a dog. In 7 experiments the prosthesis passed of its own will, and epithelization took place.

Museneeck's experiments published in 1926, represent a distinct advance. He operated on a larger number of dogs than any one before him. Museneeck emphasized the fact that the duodenum was found in each postmortem examination to be plastered against the liver. Curiously enough this phenomenon emphasized by Cahen in a clinical report in 1913 was not observed in animal experiments until the reports of Museneeck.

Museneeck operated on 53 dogs. In a group of 25 he attempted vein transplantation. The results were so poor as not to justify an attempt at analysis.

In another group of 28 dogs he made cuff excisions in 9, and in the rest either a typical or a modified Sullivan operation. His mortality was high. In a group of 7 Sullivan operations, 6 died of peritonitis between the third and ninth postoperative days. Of 28 animals, 26 developed stenosis, and in these there was not found a trace of epithelization. In only 2 dogs did there not develop a stenosis. Museneeck was much impressed by the fact that in these two the tubes remained *in situ*. They showed no infection of bile. The duodenum, as in the rest of his animals, was plastered up against the liver. The "new ducts" were

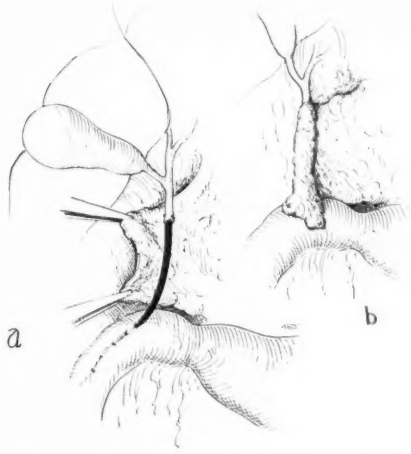

Fig. 1, a and b. Technique of application of tube.

therefore quite short, about 2 centimeters in length. They were lined by epithelium, but whether this was new or old epithelium brought together, the author did not feel certain. He was not sure that one was justified in speaking of a "new duct." So long as the tube remained *in situ*, the danger of stenosis was lessened. He would therefore advise that the tube be made to stay in as long as possible.

PERSONAL EXPERIMENTS

A comparison of results obtained in reconstructive work on the bile ducts in the two fields, the clinical and the experimental, reveals that they were much inferior in the latter. The reason assigned was the smallness and the delicacy of these structures in the experimental animal. While this is true, it may be pointed out that while the surgeon is frequently called upon to operate in the presence of baffling adhesions, cholæmic bleeding, and inflammatory states, the experimenter is always operating in a clean field and upon normal structures. Schrager and Ivy have correctly pointed out that a special knowledge of conditions as they obtain in a dog, and an adoption of a suitable technique are just as essential to success here as elsewhere.

The number of successful experiments in any one report was too small to justify drawing conclusions therefrom. Frequently post-

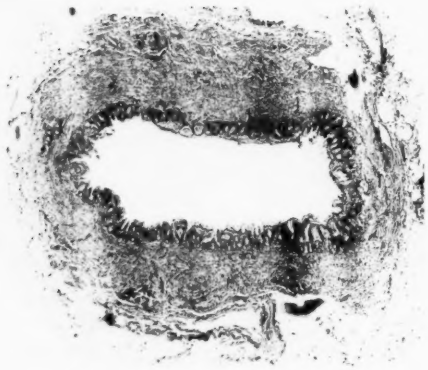

Fig. 2. Transverse section, dog 8.

Fig. 3. Transverse section, dog 21.

mortem examinations lacked accuracy, and only in a few instances were there histological examinations made. Sullivan subjected to a histological study only one specimen, although he had 8 surviving animals. For some reason he had the specimen removed on the tenth postoperative day—a period entirely too brief to test the regenerative capacity of epithelium. The pathologist's report is ambiguous on the crucial point. He states that the midportion of the new duct consisted of peritoneal tissues, whereas the question in point is whether or not this tube of peritoneal tissue (omentum) was lined by epithelium.

Horsley submitted one "new duct" (23 dogs) to a histological study, and declared that it was at least partly lined by new "columnar" epithelium. Young epithelium is cuboidal; columnar epithelium suggests mature cells.

Seulberger and Poellwein do not state the exact number but seem to have made a histological study of several specimens. These authors have not observed any effort on the part of the epithelium to proliferate.

Museneeck operated on more dogs than any experimenter in the field before him. His postmortem observations were characterized by greater accuracy. He did not miss the importance of adhesions and reports that the duodenum in every case was adhered to the liver. On the other hand, Museneeck, together with the rest of the experimenters, apparently never observed a duodenal ulcer, though he had an unusually large number of postoperative stenoses of the bile duct. In my animals the incidence of duodenal ulceration among those exhibiting varying degrees of bile duct stenosis was very high.

An attempt was made in my own work to obtain a sufficiently large number of successful experiments to justify drawing conclusions therefrom. By a successful experiment I mean one in which the animal survived a typical operation, was allowed to live a suitable period of time, and was sacrificed at will. A careful postmortem examination completed each successful experiment. I have operated on 135 dogs and can report on 28 completed experiments.

The incidence of peritonitis, of death from bile leakage, of ascending infection leading to liver abscesses, was very high in the beginning of my work. Dogs are undoubtedly very sensitive to spilling of bile in the peritoneal cavity. A number of them died of bile leakage within the first 24 or 48 hours without developing signs of peritonitis. As the work progressed the ducts became considerably larger and the postoperative mortality was reduced to an insignificant minimum. The use of nembutal anæsthetic (Abbott) adopted in the later period of my work, proved an important factor in the reduction of anæsthetic fatalities.

Experiments were planned so as to throw light upon the ability of ductal epithelium to proliferate and fill in large longitudinal defects (Group I), small longitudinal defects (Group II), as well as to grow along a prosthesis and fill in a transverse gap (Groups III and IV).